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(54) Title: SPLICE VARIANT OF HUMAN SODIUM III CHANNEL (HNAIII18)

(57) Abstract: Described herein is a splice variant of the human NaIII channel α subunit, designated hNaIII18. Also described are nucleotide and amino acid sequence for hNaIII18, oligonucleotide primers and probes for hNaIII18, hNaIII18 regulatory sequences, hNaIII18-specific antibodies, methods of detecting hNaIII18 proteins or nucleic acids, and methods of screening for modulators of hNaIII18 expression or activity.

Splice Variant of Human Sodium III Channel (hNaIII8)

This application claims priority from U.S. Provisional Application Serial No. 60/431,794, filed December 4, 2002, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to a human splice variant of the voltage-gated sodium III channel, termed hNaIII8, as well as methods for stable expression of hNaIII8 in cell lines, and methods of use in screening for compounds that modulate sodium channel activity.

BACKGROUND OF THE INVENTION

Sodium channels are voltage-gated transmembrane proteins that are involved in the generation of action potentials in electrically excitable cells such as neurons and muscle cells. They are responsible for the cellular uptake of sodium during electrical signals in cell membranes. The channels are members of a multigene family of transmembrane proteins and are typically composed of a large transmembrane pore-forming α-subunit and three smaller accessory β-subunits (Cattrall et al., Adv Neurol 1999; 79:441-56). The primary structure of α-subunits is conserved among different sub-types and species. The α-subunit is all that is required for the channel to be fully functional, however, the β-subunits have been shown to modulate the function of the channel. Specifically, co-expression of rat $\beta1$, $\beta2$, and $\beta3$ subunits with the Na(v)1.2a α-subunits in the tsA-201 sub-clone of HEK293 cells shifted sodium channel activation and inactivation to more positive membrane potentials. The $\beta3$ subunit alone caused increased persistent sodium currents. (Qu et al., Mol Cell Neurosci 2001;18(5):570-80).

Previous studies have demonstrated numerous different types of α-subunits, which are categorized based on their sensitivity to tetrodotoxin (a toxin produced by the puffer or fugu fish). Subunits that are inhibited by nanomolar concentrations of tetrodotoxin are generally referred to as tetrodotoxin-sensitive

5   channels (TTX-S), while those that require at least micromolar concentrations for inhibition are referred to as tetrodotoxin-resistant channels (TTX-R).

Rapid entry of sodium ions into cells causes depolarization and generation of the action potential. Such entry of sodium ions through sodium channels in response to a voltage change on the plasma membrane in excitable cells

10   plays a functional role in control of neuronal excitability in the central nervous system (CNS) and peripheral nervous system (PNS).

An increase in the rate of spontaneous firing in neurons is often observed in peripheral sensory ganglia following nerve injury (Ochoa and Torebjork, Brain1980; 103(4):835-53.; Nordin et al., Pain 1984; 20(3):231-45; Matzner et al., J

15   Neurophysiol 1994;72(1):349-59; Woolf, Drugs 1994; 47 Suppl 5:1-9; discussion 46-7). It has been suggested that this hyperexcitability in neurons is due to altered sodium channel expression in some chronic pain syndromes (Tanaka et al., Neuroreport 1998; 9(6):967-72). Increased numbers of sodium channels leading to inappropriate, repetitive firing of the neurons have been reported in the tips of injured

20   axons in various peripheral nervous tissues such as the DRG, which relay signals from the peripheral receptors to the central nervous system (Waxman and Brill, Biophys J 1978; 21(2):147-60; Devor et al., Neurosci Lett 1989;102(2-3):149-54; Matzner and Devor, Brain Res 1992; 597(1):92-98). Transcripts encoding the αIII subunit, which are present at only very low levels in control DRG neurons, are expressed at moderate

25   to high levels in axotomized DRG neurons together with elevated levels of αI and αII mRNAs (Waxman et al, Brain Res Mol Brain Res 1994; 22(1-4):275-89). Conversely, transcripts of sodium channel α subnits in the sensory nervous system are down-regulated in DRG neurons following axotomy (Dib-Hajj et al., Proc Natl Acad Sci U S A. 1996; 93(25):14950-4). Furthermore, the partial efficacy of sodium

30   blocking agents is well documented in patients treated for neuropathic pain (Omana-Zapata et al., Pain 1997; 7 2(1-2):41-9; Rizzo, J Neurophysiol 1997; 77(1):236-46), providing an important link between increased sodium channel expression and

neuropathic pain. Therefore, alterations in sodium channel expression and subsequent function may be a key molecular event underlying the pathophysiology of pain after peripheral nerve injury.

5   The partial type III isoform (α-subunit) of the human sodium channel gene, SCN3A, isolated from placenta, was first described by Malo et al. (Proc Natl Acad Sci U SA 1994; 91(8):2975-9; GenBank Accession No. S69887). Two alternative isoforms, neonatal and adult forms, of SCN3A were thereafter identified in human brain tissue by Lu and Brown (J Mol Neurosci 1998;10(1):67-70; GenBank Accession Nos. AF035685 and AF035686, respectively). These isoforms contained a

10   92 amino acid insert within a region containing putative splice sites (identified through sequence homology with the rat type III brain sequence). The complete coding sequences for human SCN3A genomic DNA and mRNA (and the corresponding protein sequence) also cloned from human brain, was described by Clare et al. (Ann NY Acad Sci. 1999;868:80-3; GenBank Accession Nos. AJ251507

15   (SEQ ID NO: 3-Figure 3) and AF225987 (SEQ ID NO: 4-Figure 4, respectively).

        Most recently, in 2000, Jeong et al. submitted to GenBank an mRNA sequence encoding a splice variant of human SCN3A (Accession No. AF225987; SEQ ID NO: 5-Figure 5). The amino acid sequence of this splice variant contained a 49-amino acid insert from residues 624 to 673 (SEQ ID NO: 6 - Figure 6), when

20   compared with the sequence described by Clare et al. (*supra*).

        There remains a need in the art to identify and characterize additional human sodium channels and variants thereof, in order to assist in the identification of drug candidates that can be used to treat conditions involving or associated with over- or under-expression, or over- or under-activated sodium channels.

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SUMMARY OF THE INVENTION

        The present invention provides a novel splice variant of human sodium channel III α subunit, designated herein as "hNaIII18", having the amino acid sequence of SEQ ID NO: 2 (Figure 2).

30   The present application also provides an isolated nucleic acid having a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 2. In one embodiment, the nucleic acid has the nucleotide sequence of SEQ ID NO: 1 (Figure

1). In another embodiment, the nucleic acid has a nucleotide sequence that is a degenerate variant of SEQ ID NO: 1. In yet another embodiment, the invention provides an isolated nucleic acid that hybridizes under stringent conditions to a nucleic acid having the nucleotide sequence of SEQ ID NO: 1, and preferably encodes

5   a protein having the same function as a protein having the amino acid sequence of SEQ ID NO: 2.

The isolated nucleic acid encoding hNaIII18 can be a part of a recombinant vector, e.g., for cloning, expression, and/or expansion. An expression vector comprises the nucleic acid encoding hNaIII18 operably associated with an

10   expression control sequence. The invention further provides host cells containing such a vector, and methods for producing the hNaIII18 subunit polypeptide using such host cells.

In addition, the invention provides an isolated nucleic acid oligonucleotide, such as a primer or probe, of at least 10 bases, more particularly of at

15   least 20, and more particularly of at least 30 bases, which oligonucleotide has a nucleotide sequence identical to a corresponding nucleotide sequence of the same number of contiguous bases in SEQ ID NO: 1, or its complement, which nucleotide sequence is unique and specific to the nucleotide sequence of SEQ ID NO: 1, and/or different from corresponding oligonucleotide sequences encoding known sodium

20   channel subunits. The invention also provides an antibody that preferentiallyh binds the hNaIII18 subunit protein of the invention compared to other known sodium channel subunits.

The present invention further provides a method for detecting expression of hNaIII18 in a cell or sample derived from a cell, which method

25   comprises: (i) detecting mRNA encoding hNaIII18 in a cell or in a sample derived from a cell suspected of expressing hNaIII18; or (ii) detecting hNaIII18 protein in a cell or in a sample derived from a cell with an antibody of the invention.

The present invention further provides an assay system for identifying modulators of hNaIII18 subunit containing sodium channels. The assay system

30   comprises at least one cell genetically engineered to express or overexpress hNaIII18 as part of a functional sodium channel, which can be used to screen for and thereby identify modulators of a hNaIII18-containing sodium channel. In a preferred

embodiment, cells useful in conducting the assay are mammalian cells useful in such screening methods including, *e.g.*, human embryonic kidney cells such as HEK293 cells, or cells such as *Xenopus* cells

BRIEF DESCRIPTION OF THE DRAWINGS

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Figure 1 shows the cDNA sequence of hNaIII18 of the present invention.

Figure 2 shows the amino acid sequence of hNaIII18 of the present invention.

10   **Figure 3** shows the cDNA sequence of human SCN3A of Clare et al. (*supra*) (GenBank Accession No. AJ251507).

Figure 4 shows the amino sequence of human SCN3A of Clare et al. (*supra*) (GenBank Accession No. AJ251507).

Figure 5 shows the cDNA of a human sodium channel α-subunit

15   variant by Jeong et al. (GenBank Accession No. AF225987).

Figure 6 shows the amino acid sequence a human sodium channel α-subunit variant by Jeong et al. (GenBank Accession No. AF225987).

Figure 7 shows a cDNA alignment of the hNaIII18 of the present invention, with that of the human SCN3A of Clare et al. (*supra*), and that of Jeong et

20   al. (*supra*)

Figure 8 shows the amino acid alignment of the hNaIII18 of the present invention, with that of the human SCN3A of Clare et al. (*supra*), and that of Jeong et al. (*supra*)

Figure 9A-D shows results of electrophysiology of hNaIII18-

25   transfected HEK293 cells. Figure 9A demonstrates the activation threshold voltage; Figure 9B, the steady state V ½ inactivation voltage; Figure 9C, the recovery time after inactivation; and Figure 9D, the inactivation kinetics.

DETAILED DESCRIPTION OF THE INVENTION

30   The present invention is based, in part, on the discovery of a splice variant of the human NaIII channel α subunit. The human NaIII α subunit isoform, designated herein as "hNaIII18", was cloned by RT-PCR from human embryonic

brain total RNA (Clontech, Palo Alto, CA), using human NaIII specific primers. Primers were designed from a sequence identified by searching the NCBI Human Genome database, using the human NaIII mRNA sequence (GenBank accession no. AJ251507) using reverse-transcriptase PCR (RT-PCR). PCR fragments were cloned
5   into the mammalian expression vector and the complete DNA sequence was determined.

The hNaIII18 sequence of the invention contains an additional 147 nucleotides that do not appear in the human NaIII cDNA mentioned above (SEQ ID NO: 3). Splicing in this region (nucleotides +9 to +96) had been described for the rat
10   NaIII sodium channel, but not for the human NaIII channel when this work was initiated. The nucleotide sequence of Jeong et al. 2000, *supra*, also containing the 147 nucleotide insert and encoding an amino acid sequence similar to that of SEQ ID NO: 2, was deposited in GenBank (Accession No. AF225987, SEQ ID NO: 5), and is described in International PCT publication WO 01/96552 (in Japanese). The novel
15   sequence (SEQ ID NO: 1) presented herein differs from that of SEQ ID NO:5 by 37 nucleotides out of 6093 aligned. None of the differences are found within the 147-nucleotide insertion. The amino acid sequence presented herein in SEQ ID NO: 2, differs from the SEQ ID NO:5 amino acid sequence by 12 amino acids out of 2000, with none of the differences being found in the region containing the 49 amino acid
20   insert.

Transient transfection of the novel splice variant of the invention (SEQ ID NO: 1) results in expression of functional sodium channels in mammalian cells (cell line HEK293). Stable transfection and expression of the hNaIII18 also was achieved in HEK293 cells.

25   Protein expression was confirmed in the stably transfected HEK293 cells by immunocytochemistry and Western blotting. A protein having a size of about 220 kD protein, corresponding to the expected molecular weight of hNaIII18 was identified. Functional hNaIII18 activity was confirmed by electrophysiology.

Thus, the present invention advantageously provides hNaIII18 protein,
30   including fragments and derivatives thereof; hNaIII18-encoding nucleic acids, and portions thereof including oligonucleotide primers and probes surrounding and within the region containing the 147 nucleotide insert, and hNaIII18 regulatory sequences;

hNaIII18-specific antibodies; and related methods of using these materials to detect the presence of hNaIII18 proteins or nucleic acids.

The present invention also provides an assay method for screening to identify selective modulators of hNaIII18-containing sodium ion channel activity. The method involves detecting whether a test compound increases or decreases the activity of the sodium channel, as determined, *e.g.*, by measuring current phase (electrophysiology) and ion selectivity. The assay method is preferably conducted using at least one host cell that expresses or overexpresses a functional sodium channel comprising hNaIII18, or a membrane preparation prepared therefrom. In one embodiment, the test compound inhibits (antagonizes) the activity of the sodium channel. In another embodiment, the test compound potentiates (agonizes) the activity of the sodium channel. The test system preferably involves the use of an appropriate cell culture medium to permit cell growth and viability, as well as tissue culture plates or arrays containing the host cells in the cell culture medium. In specific embodiments, host cells are mammalian cell lines such as, *e.g.*, the HEK293 cell line, although appropriate cells from other organisms, such as, *e.g.*, *Xenopus* cells, can alternatively be utilized.

The specification and figures include the following nucleotide or amino acid sequences: hNaIII18 polynucleotide (SEQ ID NO:1); hNaIII18 amino acid sequence (SEQ ID NO:2); SCN3A nucleotide sequence (SEQ ID NO:3; Clare et al., *supra*; GenBank AJ251507); SCN3A amino acid sequence (SEQ ID NO:4; Clare et al., *supra*; GenBank AJ201507); SCN3A splice variant nucleotide sequence (SEQ ID NO:5; Jeong et al., *supra*; GenBank AF225987); SCN3A splice variant amino acid sequence (SEQ ID NO:6; Jeong et al., *supra*; GenBank AF225987); forward primer utilized in Example 1 (SEQ ID NO:7); and reverse primer utilized in Example 1 (SEQ ID NO:8).

General Definitions

The following definitions are provided for clarity and illustrative purposes only, and are not intended to limit the scope of the invention.

As used herein, the term "isolated" means that the referenced material is removed from the environment in which it is normally found. Thus, an isolated

biological material can be free of cellular components, *i.e.,* components of the cells in which the material is found or produced in nature. In the case of nucleic acid molecules, an isolated nucleic acid includes a PCR product, an mRNA, a cDNA, or a restriction fragment. In another embodiment, an isolated nucleic acid is preferably

5   excised from the chromosome in which it may be found, and more preferably is no longer joined to non-regulatory, non-coding regions, or to other genes, located upstream or downstream of the gene contained by the isolated nucleic acid molecule when found in the chromosome. In yet another embodiment, the isolated nucleic acid lacks one or more naturally occurring introns. Isolated nucleic acid molecules include

10   sequences inserted into plasmids, cosmids, artificial chromosomes, phages and the like. Thus, in a specific embodiment, a recombinant nucleic acid is an isolated nucleic acid. An isolated protein may be associated with other proteins or nucleic acids, or both, with which it associates in the cell, or with cellular membranes if it is a membrane-associated protein. A protein expressed from a vector in a cell,

15   particularly a cell in which the protein is normally not expressed, is also a regarded as isolated. An isolated organelle, cell, or tissue is removed from the anatomical site in which it is found in a cell or an organism. An isolated material may be, but need not be, purified. As used herein to refer to nucleic acids, the term "isolated" does not encompass man-made genomic or cDNA libraries.

20   The term "purified" as used herein refers to material that has been isolated under conditions that reduce or eliminate the presence of unrelated materials, *i.e.,* contaminants, including native materials from which the material is obtained. For example, a purified protein is preferably substantially free of other proteins or nucleic acids with which it is associated in a cell; a purified nucleic acid molecule is

25   preferably substantially free of proteins or other unrelated nucleic acid molecules with which it can be found within a cell. As used herein, the term "substantially free" is used operationally, in the context of analytical testing of the material. Preferably, purified material substantially free of contaminants. Purity can be evaluated by chromatography, gel electrophoresis, immunoassay, composition analysis, biological

30   assay, and other methods known in the art.

           Methods for purification are well-known in the art. For example, nucleic acids can be purified by precipitation, chromatography (including preparative

solid phase chromatography, oligonucleotide hybridization, and triple helix chromatography), ultracentrifugation, and other means. Polypeptides and proteins can be purified by various methods including, without limitation, preparative disc-gel electrophoresis, isoelectric focusing, HPLC, reversed-phase HPLC, gel filtration, ion

5   exchange and partition chromatography, precipitation and salting-out chromatography, extraction, and countercurrent distribution. For some purposes, it is preferable to produce the protein in a recombinant system so that it contains an additional sequence tag that facilitates purification, such as, but not limited to, a polyhistidine sequence (His®-tag; Novagen, Madison, WI), or a sequence that

10   specifically binds to an antibody, such as the FLAG® tag (Sigma, St. Louis, MO), HA-tag (Roche Diagnostics, Indianapolis, IN), or that can be column-purified such as via the use of glutathione-S-transferase (GST). The polypeptide can then be purified from a crude lysate of the host cell by chromatography on an appropriate solid-phase matrix. Alternatively, antibodies produced against the protein or against peptides

15   derived therefrom can be used as purification reagents. Cells can be purified by various techniques, including centrifugation, matrix separation (e.g., nylon wool separation), panning and other immunoselection techniques, depletion (e.g., complement depletion of contaminating cells), and cell sorting (e.g., fluorescence activated cell sorting (FACS)). Other purification methods are possible. A purified

20   material may contain less than about 50%, preferably less than about 75%, and most preferably less than about 90%, by weight of the cellular components with which it was originally associated. The "substantially pure" indicates the highest degree of purity that can be achieved using conventional purification techniques known in the art.

25   In a specific embodiment, the term "about" or "approximately" means plus or minus 10% of the stated numerical value or range.

              As use herein, the term "ion channel" refers to a transmembrane pore that presents a hydrophilic channel for ions to cross a lipid bilayer down their electrochemical gradients. In a preferred embodiment, the ion channel is a voltage-

30   gated sodium ion channel. A "sodium channel" is an ion channel that is selective for sodium ions.

A "sample" as used herein refers to a biological material that can be obtained and tested for the presence or expression of: (i) an hNaIII18 subunit-containing ion channel; or (ii) an hNaIII18 subunit protein; or (iii) an hNaIII18 subunit-encoding nucleic acid. Such samples can be obtained from animal, preferably

5   mammalian, and more preferably human subjects, and include tissue samples, especially CNS or PNS tissues, as well as cell cultures derived from such tissues. Alternatively, such samples can comprise cells genetically engineered to express or overexpress an hNaIII18 subunit-containing ion channel or an hNaIII18 subunit protein. Such cells are preferably eukaryotic, but may alternatively be prokaryotic

10   cells. Eukaryotic cells are preferably mammalian cells, but may alternatively be *Xenopus* cells.

Non-human animals include, without limitation, laboratory animals such as mice, rats, rabbits, hamsters, guinea pigs, etc.; domestic animals such as dogs and cats; and farm animals such as sheep, goats, pigs, horses, and cows.

15   The term "modulator" refers to a compound that binds to an ion channel comprising the hNaIII18 subunit protein of the invention and differentially affects the activity of the ion channel in response to a stimulus that normally activates the function of that ion channel when compared to the activity of the ion channel not contacted with the compound. Ion channel activity can be measured, *e.g.*, using

20   electrophysiological techniques, or according to other known methods in the art. In a preferred embodiment, the ion channel is a sodium channel.

The terms "inhibitor" and antagonist refer to a compound that binds to the ion channel comprising hNaIII18, and blocks, inhibits, impedes or reduces the activity of that ion channel.

25   An "agonist" is defined as a compound that binds to the ion channel comprising hNaIII18, and promotes, enhances, stimulates or potentiates the normal biological function of the sodium channel. A "partial agonist" binds as to the ion channel or a subunit thereof, as does a full agonist, but promotes only partial function.

As used herein the term "transfected cell" or "transformed cell" refers

30   to a host cell that has been genetically engineered to express or overexpress a nucleic acid encoding a hNaIII18 subunit, preferably in combination with one or more β subunits such as, *e.g.*, β-subunits 1-3 as described in GenBank Accession Nos.

U87445, AF007783, AH005825, AF007783, AF04948, L10338 and L16242, among others. Any cell can be used, preferably a eukaryotic cell, and more preferably a vertebrate cells, preferably a mammalian cell, or a *Xenopus* cell. Such cells additionally can be genetically engineered to coexpress or overexpress a different

5   sodium channel subunit. Such genetically engineered cells include those cells into which one or more heterologous hNaIII18-encoding nucleic acids have been introduced and are expressed or overexpressed. Such genetically engineered cells also include those cells engineered to express or overexpress one or more endogenous hNaIII18 subunits, for example, by gene activation technology.

10   Such cells are particularly suitable to conduct an assay to screen for compounds that modulate the function of the hNaIII18 subunit-containing sodium channel in response to an appropriate stimulus (*e.g.*, TTX). An "assay method" typically makes use of one or more such cells, *e.g.*, in a microwell plate or some other culture system. The effects of a test compound can be determined on a single cell or

15   on a collection of cells sufficient to allow measurement of ionic current, activation threshold, or ionic permeability characteristics of the hNaIII18 subunit-containing sodium channels. For example, single cells can be tested, *e.g.*, by use of patch clamp or other appropriate electrophysiological techniques.

             A "test compound" or "candidate compound" is any molecule that can

20   be tested for its ability to bind to the hNaIII18 subunit-containing sodium channel,or to a subunit thereof, and preferably modulate on the activity of the hNaIII18 subunit-containing sodium channel. A compound that binds and modulates a hNaIII18 subunit-containing sodium channel is a "lead compound" suitable for further testing and development.

25   The term "ligand" can alternatively be used to refer to any compound or peptide or polypeptide that binds to and modulates the activity of a hNaIII18 subunit, or a sodium channel comprising hNAIII18.

             The term "pain disorder" includes chronic pain, defined as pain lasting longer than one month (Bonica, Semin Anesth 1986, 5:82-99), and is characterized by

30   unrelenting persistent pain that is not amenable to routine pain control methods. The term "pain disorder" also includes neuropathic pain and nociceptive pain.

"Chronic pain" can be defined as pain lasting longer than one month (Bonica, Semin Anesth 1986, 5:82-99), and is characterized by unrelenting persistent pain that is not amenable to routine pain control methods. Chronic pain includes, but is not limited to, inflammatory pain, postoperative pain, cancer pain, osteoarthritis

5   pain associated with metastatic cancer, trigeminal neuralgia, acute herpetic and postherpetic neuralgia, diabethic neuropathy, causalgia, brachial plexus avulsion, occipital neuralgia, reflex sympathetic dystrophy, fibromyalgia, gout, phantom limb pain, burn pain, pain associated with spinal cord injury, multiple sclerosis, reflex sympathetic dystrophy and lower back pain and other forms of neuralgia, neuropathic,

10   and idiopathic pain syndromes.

"Neuropathic pain" can be caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from

15   chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiences. Neuropathic pain includes but is not limited to pain caused by nerve injury such as, for example, the pain from which diabetics suffer.

Chronic and neuropathic types of pain generally arises from injury to the peripheral or central nervous tissue.

20   "Nociceptive pain" is due to activation of pain-sensitive nerve fibers, either somatic or visceral. Nociceptive pain generally results as a response to direct tissue damage. The initial trauma causes the release of several chemicals including bradykinin, serotonin, substance P, histamine, and prostaglandin. When somatic nerves are involved, the pain is typically experienced as aching or pressure-like.

25

Molecular Biology Definitions

In accordance with the present invention there may be employed conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art. See, *e.g.,* Sambrook, Fritsch & Maniatis, Molecular

30   Cloning: A Laboratory Manual, Second Edition (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (herein "Sambrook et al., 1989"); DNA Cloning: A Practical Approach, Volumes I and II (D.N. Glover ed. 1985);

Oligonucleotide Synthesis (M.J. Gait ed. 1984); Nucleic Acid Hybridization [B.D. Hames & S.J. Higgins eds. (1985)]; Transcription And Translation [B.D. Hames & S.J. Higgins, eds. (1984)]; Animal Cell Culture [R.I. Freshney, ed. (1986)]; Immobilized Cells And Enzymes [IRL Press, (1986)]; B.Perbal, A Practical Guide To

5   Molecular Cloning (1984); F.M. Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, Inc. (1994).

"Amplification" of DNA as used herein denotes the use of exponential amplification, techniques such as polymerase chain reaction (PCR), and non-exponential amplification, such as linked linear amplification, to increase the

10   concentration of a particular DNA sequence within a mixture of DNA sequences. For a description of PCR see Saiki et al., Science 1988, 239:487. For a description of linked linear amplification, see U.S. Patent Nos. 6,335,184 and 6,027,923 and Reyes et al. Clinical Chemistry 2001; 47: 131-40; Wu et al. Genomics 1989; 4: 560-569.

As used herein, "sequence-specific oligonucleotides" refers to related

15   sets of oligonucleotides that can be used to detect allelic variations or mutations in the hNaIII18 gene, or can be used for amplification of an hNAIII18 encoding-nucleic acid.

The nucleic acid molecules (polynucleotides) described herein may be flanked by natural regulatory (expression control) sequences, or may be associated

20   with heterologous sequences, including promoters, internal ribosome entry sites (IRES) and other ribosome binding site sequences, enhancers, response elements, suppressors, signal sequences, polyadenylation sequences, introns, 5'- and 3'- non-coding regions, and the like. The nucleic acid molecules may also be modified by many means known in the art. Non-limiting examples of such modifications include

25   methylation, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, and internucleotide modifications such as, for example, replacement with uncharged linkages (*e.g.,* methyl phosphonates, phosphotriesters, phosphoroamidates, carbamates, etc.) and with charged linkages (*e.g.,* phosphorothioates, phosphorodithioates, etc.). Polynucleotides may contain one or

30   more additional covalently linked moieties, such as, for example, proteins (*e.g.,* nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), intercalators (*e.g.,* acridine, psoralen, etc.), chelators (*e.g.,* metals, radioactive metals, iron, oxidative

metals, etc.), and alkylators. The polynucleotides may be derivatized by formation of a methyl or ethyl phosphotriester or an alkyl phosphoramidate linkage. Furthermore, the polynucleotides herein may also be modified with a label capable of providing a detectable signal, either directly or indirectly. Exemplary labels include radioisotopes, fluorescent molecules, biotin, and the like.

A "coding sequence" or a sequence "encoding" an expression product, such as an RNA, polypeptide, protein, or enzyme, is a nucleotide sequence that, when expressed, results in the production of that RNA or polypeptide, *i.e.,* the nucleotide sequence encodes an amino acid sequence for that polypeptide. A coding sequence or "open reading frame (ORF)" for a polypeptide will typically include a start codon (usually ATG) and a stop codon.

The term "gene", also called a "structural gene" refers to a basic unit of hereditary material. Specifically a gene is an ordered sequence of DNA nucleotide bases that encodes one polypeptide chain (via mRNA). The gene includes regions preceding and following the coding region (such as promoter sequences, a 5'-untranslated region, and a 3'-untranslated region, which affect, for example, the conditions under which the gene is expressed) as well as (in eukaryotes) intervening sequences (introns) between individual coding segments (exons).

A "promoter sequence" is a DNA regulatory region capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. For purposes of defining the present invention, the promoter sequence is bounded at its 3' terminus by the transcription initiation site and extends upstream (5' direction) to include the minimum number of bases or elements necessary to initiate transcription at levels detectable above background. Within the promoter sequence will be found a transcription initiation site (conveniently defined for example, by mapping with nuclease S1), as well as protein binding domains (consensus sequences) responsible for the binding of RNA polymerase. The present invention includes the hNaIII18 gene promoter found in the genome, which can be operatively associated with a hNaIII18 coding sequence with a heterologous coding sequence.

The term "host cell" means any cell of any organism that is selected, modified, transformed, grown, or used or manipulated in any way, for the production

of a substance by the cell, for example, the expression by the cell of a gene, a DNA or RNA sequence, or a polypeptide. Host cells can further be used for screening or other assays, as described *infra*.

A coding sequence is "under the control of" or "operatively associated with" transcriptional and translational control sequences in a cell when such control sequences operate to effect RNA polymerase transcription of the coding sequence into mRNA, which is then trans-RNA spliced (if it contains introns) and translated, in the case of mRNA, into the protein encoded by the coding sequence.

The terms "express" and "expression" mean allowing or causing the information in a gene or cDNA or mRNA sequence to become manifest, for example, by producing a protein by activating the cellular functions involved in transcription and translation of a corresponding gene, cDNA or mRNA sequence. A gene or cDNA sequence is expressed in or by a cell to form an "expression product" such as a protein. The expression product itself, *e.g.*, the resulting protein, may also be said to be "expressed" by the cell. An expression product can be characterized as intracellular, extracellular, transmembrane, or secreted depending on the particular product. The hNaIII18 subunit protein of the invention is typically expressed as a transmembrane protein with intracellular and extracellular domains.

The term "transfection" means the introduction of a "foreign" (*i.e.*, extrinsic or extracellular) gene, DNA or RNA sequence into a host cell so that the host cell will express the introduced gene or sequence to produce a desired substance, typically a protein encoded by the introduced gene or sequence. The introduced gene or sequence may also be called a "cloned" or "foreign" or "heterologous" gene or sequence, and may include regulatory or control sequences, such as start, stop, promoter, signal, secretion, or other sequences used by a cell's genetic machinery. The gene or sequence may include non-functional sequences or sequences with no known function.

The term "transformation" refers to the process by which DNA is introduced from the surrounding medium into a prokaryotic host cell.

The term "transduction" refers to the introduction of DNA into a prokaryotic host cell via a bacterial virus, or bacteriophage.

        A prokaryotic or eukaryotic host cell that receives and expresses introduced DNA or RNA has been "transformed" and is a "transformant" or a "clone." The DNA or RNA introduced into a host cell can come from any source, including cells of the same genus or species as the host cell, or cells of a different genus or

5   species, or synthetic sequences.

        The transformed cells of the invention are particularly suitable for an assay system for the detection of compounds that modulate the function of hNaIII18 subunit-containing sodium channels in response to activation, e.g., in response to exposure TTX. An "assay method" makes use of one or more such cells, e.g., in a

10   microwell plate or some other culture or assay system to permit evaluation of the effects of a test compound on the cell(s), e.g., by measuring ionic current or activation threshold characteristics of the hNaIII18 subunit-containing sodium channel.

        The term "recombinantly engineered cell" refers to any prokaryotic or eukaryotic cell that has been manipulated to express or overexpress the hNaIII18

15   subunit by any appropriate method, including transfection, transformation or transduction. This term also includes endogenous activation of a hNaIII18 gene in a cell that does not normally express hNaIII18 or that expresses the protein at a sub-optimal level.

        The terms "vector", "cloning vector" and "expression vector" mean the

20   vehicle by which a DNA or RNA sequence (e.g., a foreign gene) can be introduced into a host cell, so as to transform the host and promote expression (e.g., transcription and translation) of the introduced sequence. Vectors include plasmids, cosmids, phages, viruses, etc.; they are discussed in greater detail below.

        Vectors typically comprise the DNA of a transmissible agent, into

25   which foreign DNA is inserted. A common way to insert one segment of DNA into another segment of DNA involves the use of restriction enzymes to cleave DNA at specific restriction sites. A "cassette" refers to a DNA coding sequence or segment of DNA that codes for an expression product that can be inserted into a vector at defined restriction sites. The cassette restriction sites are designed to ensure insertion of the

30   cassette in the proper reading frame. Generally, foreign DNA is inserted at one or more restriction sites of the vector DNA, and then is carried by the vector into a host cell along with the transmissible_vector DNA. A segment or sequence of DNA

having inserted or added DNA, such as an expression vector, can also be called a "DNA construct." A common type of vector is a plasmid. A plasmid vector often contains coding DNA and promoter DNA and has one or more restriction sites suitable for inserting foreign DNA. Coding DNA is a DNA sequence that encodes a

5   particular amino acid sequence for a particular protein. Promoter DNA is a DNA sequence that initiates, regulates, or otherwise mediates or controls the expression of the coding DNA. Promoter DNA and coding DNA may be from the same gene or from different genes, and may be from the same or different organisms. A large number of vectors, including plasmid and fungal vectors, have been described for

10   replication and/or expression in a variety of eukaryotic and prokaryotic hosts. Non-limiting examples include pKK plasmids (Clonetech), pUC plasmids, pET plasmids (Novagen, Inc., Madison, WI), pRSET or pREP plasmids (Invitrogen, San Diego, CA), or pMAL plasmids (New England Biolabs, Beverly, MA), and many appropriate host cells. Recombinant cloning vectors will often include one or more replication

15   systems for cloning or expression, one or more markers for selection in the host, *e.g.,* antibiotic resistance, and one or more expression cassettes.

The term "expression system" means a host cell and compatible vector under suitable conditions, *e.g.,* for the expression of a protein coded for by foreign DNA carried by the vector and introduced to the host cell. Common expression

20   systems include *E. coli* host cells and plasmid vectors, insect host cells and baculovirus vectors, and mammalian host cells and vectors.

The term "heterologous" refers to a combination of elements not naturally occurring. For example, heterologous DNA refers to DNA not naturally present in that cell. Alternativley, heterologous DNA refers to combinations of

25   sequences that do not naturally occur together in that cell, *e.g.,* promoter sequences from a gene from one cell type linked to coding sequences of a gene that is not normally controlled by that promoter or expressed by another cell type. Preferably, the heterologous DNA includes a gene foreign to the cell. A heterologous expression regulatory element is such an element operatively associated with a different gene

30   than the one it is operatively associated with in nature. In the context of the present invention, a hNaIII18 gene is heterologous to the vector DNA in which it is inserted

for cloning or expression purposes, and is heterologous to a host cell containing such a vector in which it is expressed, *e.g.,* a HEK cell.

The terms "mutant" and "mutation" mean any detectable change in genetic material, *e.g.,* DNA, or any process, mechanism, or result of such a change. This includes gene mutations in which the structure (*e.g.,* DNA sequence) of a gene is altered; any gene or DNA arising from any mutation process; and any expression product (*e.g.,* protein or enzyme) expressed by a non-silent modification of a gene or DNA sequence. The term "variant" may also be used to indicate a modified or altered gene, DNA sequence, polypeptide, cell, etc., *i.e.,* any kind of mutant therefrom.

"Sequence-conservative variants" or "degenerate variants" of a polynucleotide sequence are those in which a change of one or more nucleotides in a given codon position results in no alteration in the amino acid encoded at that position.

"Function-conservative variants" are those in which a given amino acid residue in a protein has been changed without substantially altering the function of the polypeptide, including, but not limited to, replacement of an amino acid with a residue having similar properties (such as, for example, polarity, hydrogen bonding potential, acidic, basic, hydrophobic, aromatic, and the like). Amino acids with similar properties are well known in the art. For example, arginine, histidine and lysine are hydrophilic-basic amino acids and may be interchangeable. Similarly, isoleucine, a hydrophobic amino acid, may be replaced with leucine, methionine or valine. Such changes are expected to have little or no effect on the apparent molecular weight, isoelectric point, or function of the protein. Amino acid residues may be varied in a protein so that the percent amino acid sequence identity between the original protein and the variant may be, for example, at least 70%, 80%, 90%, 95% or 99%, as determined according to a default alignment scheme such as by the Cluster Method, wherein similarity is based on the MEGALIGN algorithm, or BLAST. A "function-conservative variant" of the present invention includes those polypeptides having the above-described amino acid sequence identities , and having the same or substantially similar functions as the native or parent hNaIII18 subunit protein of the invention

As used herein, the term "homologous" refers to the relationship between proteins that possess a "common evolutionary origin," including proteins

from superfamilies (*e.g.*, the immunoglobulin superfamily) and homologous proteins

from different species (*e.g.*, myosin light chain, etc.) (Reeck et al., Cell 1987, 50:667).

Such proteins (and their encoding genes) have sequence homology, as reflected by

their sequence similarity or sequence identity, whether in terms of percent similarity

5   or the presence of specific residues or motifs at conserved positions.

Accordingly, the term "sequence similarity" or "sequence identity"

refers to the degree of identity or correspondence between nucleic acid or amino acid

sequences of proteins that may or may not share a common evolutionary origin (see

Reeck et al., *supra*). However, in common usage and in the instant application, the

10   term "homologous," when modified with an adverb such as "highly," may refer to

sequence similarity and may or may not relate to a common evolutionary origin.

In a specific embodiment, two DNA sequences are "substantially

homologous" or "substantially similar" when at least about 80%, and most preferably

at least about 90, 95% or 99% of the nucleotides match over the defined length of the

15   DNA sequences, as determined by sequence comparison algorithms, such as BLAST,

FASTA, DNA Strider, etc. An example of such a sequence is an allelic or species

variant of the specific hNaIII18 gene of the invention. Sequences that are

substantially homologous can be identified by comparing the sequences using

standard software available in sequence data banks, or in a Southern hybridization

20   experiment under, for example, stringent conditions as defined for that particular

system.

Similarly, in a particular embodiment, two amino acid sequences are

"substantially homologous" or "substantially similar" when greater than 80%, 90%,

95% or 99% of the amino acids are identical. Preferably, the similar or homologous

25   sequences are identified by alignment using, for example, the GCG (Genetics

Computer Group, Program Manual for the GCG Package, Version 7, Madison,

Wisconsin) pileup program, or any of the programs described above (BLAST,

FASTA, etc.).

A nucleic acid molecule is "hybridizable" to another nucleic acid

30   molecule, such as a cDNA, genomic DNA, or RNA, when a single stranded form of

the nucleic acid molecule can anneal to the other nucleic acid molecule or its

complement under the appropriate conditions of temperature and solution ionic

strength (see Sambrook *et al.*, *supra*). The conditions of temperature and ionic strength determine the "stringency" of the hybridization. For preliminary screening for homologous nucleic acids, low stringency hybridization conditions, using a Tm (melting temperature) in the range of about 55°C with low salt and/or denaturant concentrations, can be used, *e.g.*, 5x SSC, 0.1% SDS, 0.25% milk, and no formamide; or 30% formamide, 5x SSC, 0.5% SDS. Moderate stringency hybridization conditions correspond to use of a higher Tm, and higher concentrations of salt and/or denaturants, *e.g.*, 40% formamide, with 5x or 6x SSC. High stringency hybridization conditions correspond to the highest Tm and concentrations of salt/and/or denaturants, *e.g.*, 68°C, 50% formamide, 5x or 6x SSC. SSC is a 0.15M NaCl, 0.015M Na-citrate buffer. Hybridization requires that the two nucleic acids contain complementary sequences, although depending on the stringency of the hybridization, mismatches between bases are possible. The appropriate stringency for hybridizing nucleic acids depends on the length of the nucleic acids and the degree of complementation, as known in the art. The greater the degree of similarity or homology between two nucleotide sequences, the higher the value of Tm for hybrids of nucleic acids having those sequences. The relative stability (corresponding to higher Tm) of nucleic acid hybridizations decreases in the following order: RNA:RNA, DNA:RNA, DNA:DNA. For hybrids of greater than 100 nucleotides in length, equations for calculating Tm have been derived (see Sambrook *et al.* 1989, *supra*, 9.50-9.51). For hybridization with shorter nucleic acids, *i.e.*, oligonucleotides, the position of mismatches becomes more important, and the length of the oligonucleotide determines its specificity (see Sambrook *et al.*, *supra*, 11.7-11.8). A minimum length for a hybridizable nucleic acid is at least about 10 nucleotides; preferably at least about 15 nucleotides; and more preferably at least about 20 nucleotides.

In a specific embodiment, the term "standard hybridization conditions" refers to a Tm of 55°C, and utilizes conditions as set forth above. In a preferred embodiment, the Tm is about 60°C; in a more preferred embodiment, the Tm is about 65°C. In a specific embodiment, "high stringency" refers to hybridization and/or washing conditions at 68°C, in 0.2 x SSC, at 42°C in 50% formamide, 4x SSC, or under conditions that afford levels of hybridization equivalent to those observed under either of these two conditions.

As used herein, the term "oligonucleotide" refers to a nucleic acid, generally of at least 10, preferably at least 15, and more preferably at least 20 nucleotides, preferably no more than 100 nucleotides, that is hybridizable to a genomic DNA molecule, a cDNA molecule, or an mRNA molecule, or other nucleic

5   acid of interest. Oligonucleotides can be labeled, e.g., with $\gamma^{32}P$-nucleotides or nucleotides to which a label, such as biotin, has been covalently conjugated. In one embodiment, a labeled oligonucleotide can be used as a probe to detect the presence of a nucleic acid. In another embodiment, oligonucleotides (one or both of which may be labeled) can be used as PCR primers, either for cloning a full length nucleic

10   acid or a fragment of a nucleic acid encoding the hNaIII18 subunit, or to detect the presence of nucleic acids encoding hNaIII18. In a further embodiment, an oligonucleotide of the invention can form a triple helix with a hNaIII18-encoding DNA molecule. Generally, oligonucleotides are prepared synthetically, preferably on a nucleic acid synthesizer. Accordingly, oligonucleotides can be prepared with non-

15   naturally occurring phosphoester analog bonds, such as thioester bonds, etc.

The present invention also provides antisense nucleic acids, which may be used to inhibit expression of the hNaIII18 subunit protein of the invention. Inhibition of hNaIII18 expression may be desired when upregulation of hNaIII18 expression or excessive activation of an hNaIII18-containing ion channel induces or

20   otherwise contributes to an increase in pain or a pain disorder in a subject.

An "antisense nucleic acid" is a single stranded nucleic acid molecule, which may be DNA, RNA, a DNA-RNA chimera, or derivatives thereof, which, on hybridizing under cytoplasmic conditions with complementary bases in an RNA or DNA molecule, inhibits the expression or translation of the encoded gene. If the

25   RNA is an mRNA transcript, the antisense nucleic acid is a counter-transcript or mRNA-interfering complementary nucleic acid. As presently used, "antisense" broadly includes RNA-RNA interactions, RNA-DNA interactions, and RNase-H mediated arrest. Antisense nucleic acid molecules can be encoded by a recombinant gene for expression in a cell (e.g., U.S. Patent No. 5,814,500; U.S. Patent No.

30   5,811,234), or alternatively they can be prepared synthetically (see, e.g., U.S. Patent No. 5,780,607).

In addition to antisense sequences, the present invention also provides ribozymes useful to inhibit hNaIII18 expression. Ribozyme technology is described further in Intracellular Ribozyme Applications: Principals and Protocols, Ed. Rossi and Couture, 1999, Horizon Scientific Press

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hNaIII18 Nucleic Acids

A polynucleotide molecule encoding hNaIII18, whether genomic DNA or cDNA, can be isolated from any source, particularly from a human cDNA or genomic library. Methods for obtaining specific polynucleotide molecules gene are

10   well known in the art, as described above (see, *e.g.,* Sambrook *et al.,* 1989, *supra*). The DNA may be obtained by standard procedures known in the art from cloned DNA (*e.g.,* a DNA "library"), and preferably is obtained from a cDNA library prepared from tissues with high level expression of the encoded protein, by chemical synthesis, by cDNA cloning, or by the cloning of genomic DNA, or fragments

15   thereof, purified from the desired cell (See, for example, Sambrook *et al.,* 1989, *supra*; Glover, D.M. (ed.), 1985, DNA Cloning: A Practical Approach, MRL Press, Ltd., Oxford, U.K. Vol. I, II). Clones derived from genomic DNA may contain regulatory and intron DNA regions in addition to coding regions. Clones derived from cDNA will not contain intron sequences. Whatever the source, the

20   polynucleotide molecule should be cloned into a vector suitable for its propagation. Identification of a specific DNA fragment containing the desired hNaIII18-encoding sequence may be accomplished in a number of ways. For example, a portion of a hNaIII18 encoding polynucleotide molecule exemplified *infra* can be purified and labeled to prepare a labeled probe, and the generated DNA library may be screened by

25   nucleic acid hybridization to the labeled probe (Benton and Davis, Science 1977, 196:180; Grunstein and Hogness, Proc. Natl. Acad. Sci. U.S.A. 1975, 72:3961). Those DNA fragments with substantial homology to the probe, such as an allelic variant from another individual, will hybridize. In a specific embodiment, highest stringency hybridization conditions are used to identify a homologous hNaIII18 gene.

30   Further selection can be carried out on the basis of the properties of the gene, *e.g.,* if the gene encodes a protein product having the same physicochemical profile (*i.e.,* isoelectric, electrophoretic, electrophysiological, amino acid composition,

partial or complete amino acid sequence, antibody binding activity, or ligand binding profile) of the hNaIII18 subunit protein disclosed herein. Thus, the presence of the nucleic acid may be detected by assays based on the physical, chemical, immunological, or functional properties of its expressed product.

5   Other DNA sequences which encode substantially the same amino acid sequence as a hNaIII18 gene may be used in the practice of the present invention. These include but are not limited to allelic variants, species variants, sequence conservative variants, and function conservative variants.

Amino acid substitutions may also be introduced to substitute an amino

10   acid with a particularly preferable property. For example, a Cys may be introduced at a potential site for disulfide bridges with another Cys.

Polynucleotide molecules encoding the hNaIII18 subunit , and the encodied polypeptide, derivatives and analogs thereof ,can be produced by various methods known in the art. The manipulations which result in their production can

15   occur at the gene or protein level. For example, the cloned hNaIII18 gene or cDNA sequence can be modified by any of numerous strategies known in the art (Sambrook *et al.*, 1989, *supra*). The sequence can be cleaved at appropriate sites with restriction endonuclease(s), followed by further enzymatic modification if desired, isolated, and ligated *in vitro*. In the production of the polynucleotide molecule encoding a

20   derivative or analog of hNaIII18, care should be taken to ensure that the modified polynucleotide sequence remains within the same translational reading frame as the hNaIII18 gene, uninterrupted by premature translational stop signals.

Additionally, the encoding nucleic acid sequence can be mutated *in vitro* or *in vivo* to create and/or destroy translation, initiation, and/or termination

25   sequences, or to create variations in coding regions and/or form new restriction endonuclease sites or destroy preexisting ones, to facilitate further *in vitro* modification. Such modifications can be made to introduce restriction sites and facilitate cloning the polynucleotide molecule into an expression vector. Any technique for mutagenesis known in the art can be used, including but not limited to,

30   *in vitro* site-directed mutagenesis (Hutchinson, C., *et al.*, J. Biol. Chem.1978; 253:6551; Zoller and Smith, DNA 1984; 3:479-488; Oliphant *et al.*, Gene 1986; 44:177; Hutchinson *et al.*, Proc. Natl. Acad. Sci. U.S.A.1986; 83:710), use of TAB

linkers (Pharmacia), etc. PCR techniques are preferred for site directed mutagenesis (see Higuchi, 1989, "Using PCR to Engineer DNA", in PCR Technology: Principles and Applications for DNA Amplification, H. Erlich, ed., Stockton Press, Chapter 6, pp. 61-70).

5   The identified and isolated polynucleotide molecule can then be inserted into an appropriate cloning vector. A large number of vector-host systems known in the art may be used. Possible vectors include, but are not limited to, plasmids or modified viruses, but the vector system must be compatible with the host cell used. Examples of vectors include, but are not limited to, *E. coli*, bacteriophages

10   such as lambda derivatives, or plasmids such as Bluescript, pBR322 derivatives or pUC plasmid derivatives, *e.g.,* pGEX vectors, pmal-c, pFLAG, etc. The insertion into a cloning vector can, for example, be accomplished by ligating the DNA fragment into a cloning vector that has complementary cohesive termini. However, if the complementary restriction sites used to fragment the DNA are not present in the

15   cloning vector, the ends of the DNA molecules may be enzymatically modified. Alternatively, any restriction site desired may be produced by ligating nucleotide sequences (linkers) onto the DNA termini; these ligated linkers may comprise specific chemically synthesized oligonucleotides encoding restriction endonuclease recognition sequences. In addition, simple PCR or overlapping PCR may be used to

20   insert a fragment into a cloning vector.

Recombinant molecules can be introduced into host cells via transformation, transfection, infection, electroporation, etc., so that many copies of the gene sequence are generated. Preferably, the cloned gene is contained on a shuttle vector plasmid, which provides for propagation in a cloning cell, *e.g., E. coli,* and

25   facile purification for subsequent insertion into an appropriate expression cell line, if such is desired. For example, a shuttle vector, which is a vector that can replicate in more than one type of organism, can be prepared for replication in both *E. coli* and *Saccharomyces cerevisiae* by linking sequences from an *E. coli* plasmid with sequences from the yeast 2Φ plasmid.

30   In a preferred embodiment of the invention, the hNaIII18 sodium channel is cloned using a strategy designed to minimize mutations during cDNA

preparation, RT-PCR amplification, and growth in bacteria. This strategy is described in detail *infra*, in Example 1. The main points are summarized as follows:

First, as an alternative to conventional reverse transcriptases, which function optimally at temperatures of between 37 °C and 43 °C, this method employs an avian RNase (-) reverse transcriptase that functions optimally at temperatures between 50-65 °C. The higher temperature serves to decrease secondary structure of the RNA to produce higher cDNA yield.

Second, for amplification of the cDNA, an enzyme mixture comprising the conventional thermostable Taq polymerase and Pwo polymerase is used. This mixture is optimized to produce very large PCR products with low error frequency, thus decreasing the mutation frequency.

Third, the number of cycles of amplification is decreased to about 28, as opposed to the typical 30-35 cycles to further reduce the possibility of mutation.

Fourth, the PCR products are electrophoresed and visualized on an agarose gel containing Crystal Violet stain, as opposed to ethidium bromide. Crystal Violet allows visualization in white light, eliminating the need for UV exposure. UV is known to induce mutations in ethidium bromide-stained DNA.

Fifth, to minimize recombination and mutation in plasmid DNA during amplification in bacteria, the PCR amplified cDNA is cloned into a low-copy number expression vector that is engineered to have limited replication cycles and contains a tetracycline-resistance gene as a selectable marker instead of an ampicillin resistance gene. Fewer replication cycles again reduces the error rate during DNA synthesis, and selection with tetracycline is less likely to induce mutations in the plasmid than is ampicillin.

Sixth, competent bacterial cells that are designed to optimize cloning of unstable inserts are selected for the transformation, and grown at a lower temperature (30-33 °C versus 37 °C) to decrease the growth rate and therefore, minimize the possibility of mutations. In addition, the cultures should be maintained in exponential (log) phase throughout growth, eliminating the possibility of mutations resulting from starvation, poor aeration, and accumulation of toxic metabolites.

Seventh, small tetracycline resistant colonies are chosen for evaluation rather than large ones. Human NaIII expression during growth is expected to be toxic to bacteria, thus transformed cells will yield smaller colonies.

hNaIII18 Regulatory Nucleic Acids

Elements of the hNaIII18 promoter can be identified by scanning the human genomic region upstream of the hNaIII18 start site, _e.g.,_ by creating deletion mutants and checking for expression, or by using an algorithm. Sequences up to about 6 kilobases (kb) or more upstream from the hNaIII18 start site can contain tissue-specific regulatory elements.

The term "hNaIII18 promoter" encompasses artificial or heterologous promoters. Such promoters can be prepared by deleting non-essential intervening sequences from the upstream region of the hNaIII18 promoter, or by joining upstream regulatory elements from the hNaIII18 promoter with a heterologous minimal promoter, such as the CMV immediate early promoter.

A hNaIII18 promoter can be operably associated with a heterologous coding sequence, _e.g.,_ for a reporter gene (luciferase and green fluorescent proteins are examples of reporter genes) in a construct. This construct can be used to test for conditions or reagents that normally result in expression. This construct can be used in screening assays, described below, for hNaIII18 agonists and antagonists.

hNaIII18 regulatory nucleic acids of the present invention also include non-endogenous or artificial promoter sequences or sequences that encode zinc finger proteins that may be used, _e.g.,_ in gene activation techniques, to initiate expression of hNaIII18 in cells where it is not normally expressed or to upregulate expression of the hNaIII18 subunit protein to a higher level where it would otherwise be expressed in suboptimal levels. Gene activation techniques that may be adapted to this use are described in the art, _e.g.,_ in U.S. Patent Nos. 5,968,502 and 6,214,622 to Treco et al.

Expression of hNaIII18 Polypeptides

The primary goal for establishing a stable cell line expressing functional human sodium channels is to identify antagonists to inhibit sodium currents

mediated by the sodium channels. DRG neurons transmit nociceptive signals from the peripheral nervous system to the central nervous system. TTX-S and TTX-R sodium channels mediate the DRG action potentials responsible for these signals. However, DRG neurons express several different isoforms of TTX-S and TTX-R

5   currents, thereby making it difficult to determine specific interactions of antagonists with particular subtypes of sodium channels in theses cells.

By generating a cell line that expresses a single sodium channel subtype, *e.g.*, hNaIII18, alone or preferably in combination with appropriate β subunits, the effect of drugs on the different sodium channel isoforms can be assessed.

10   Previously, developing stable cell lines expressing nucleic acids containing repetitive sequences, such as those contained within sodium channel genes, has been challenging. In particular, cell lines expressing functional sodium channels have been difficult to generate due to the occurrence of inactivating mutations arising in the cDNA during the cloning process (*i.e.*, cDNA preparation, PCR amplification, and

15   subsequent growth in bacteria). International PCT publication WO 98/38302 (Delgado et al.) describes isolation, cloning and expression of a rat TTX-S sodium channel in *Xenopus* oocytes. Experiments described therein demonstrate the formation of a functional TTX-S channel after injection of cRNA into *Xenopus* oocytes for the α-subunit, alone or in combination with the β1, β2 or β3 subunits.

20   International PCT Publication WO 01/68681 (Aitken et al.) describes altered ion channel proteins having acquired sensitivity or refractory sensitivity to a gating agent. A rat sodium channel type II was modified by site-directed mutagenesis and PCR to contain sequences that bind α-scorpion toxins, which inactivate sodium channels, for use to evaluate ion channel activity and to screen for compounds for therapeutic

25   applications. The modified sodium channel was then stably or transiently expressed in several mammalian host cells, including HEK293 variants and CHO cells, which were used in a high-throughput, plate-based screening assay.

International PCT publication WO/02068 (Korsgaard) describes stable cloning of a splice variant of a rat αI sodium channel in HEK293 cells.

30   To date, there have been no reports of stable expression of a cloned human sodium type III channel in mammalian cells. The method described herein combines several procedures to facilitate the cloning and generation of stable cell

lines containing such repetitive sequences, resulting in functional expression of such genes. In particular, the present invention describes the cloning and stable expression of a novel splice variant of human NaIII, designated hNaIII18.

5   The nucleotide sequence coding for hNaIII18, or an antigenic fragment, derivative or analog thereof, (including, *e.g.*, a chimeric protein) can be inserted into an appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted protein-coding sequence. Thus, a nucleic acid molecule having a nucleotide sequence encoding the hNaIII18 subunit protein of the invention can be operationally associated with a

10   promoter in an expression vector of the invention. Either a cDNA or genomic sequence can be cloned and expressed under control of such regulatory sequences. Such vectors can be used to express functional, or functionally inactivated, hNaIII18 polypeptides.

          The necessary transcriptional and translational signals can be provided

15   on a recombinant expression vector, or they may be supplied from the native gene encoding hNaIII18 and/or its flanking regions.

          Potential host-vector expression systems include but are not limited to mammalian cell systems transfected with expression plasmids or infected with virus (*e.g.*, vaccinia virus, adenovirus, adeno-associated virus, herpes virus, etc.); insect cell

20   systems infected with virus (*e.g.*, baculovirus); microorganisms such as yeast containing yeast vectors; and bacteria transformed with bacteriophage, DNA, plasmid DNA, or cosmid DNA. The expression elements of vectors vary in their strengths and specificities. Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used.

25   Expression of the hNaIII18 protein may be controlled by any promoter/enhancer element known in the art, but these regulatory elements must be functional in the host selected for expression. Promoters which may be used to control hNaIII18 gene expression include, but are not limited to, cytomegalovirus (CMV) promoter (see, *e.g.*, U.S. Patent Nos. 5,385,839 and 5,168,062), the SV40

30   early promoter region (Benoist and Chambon, Nature 1981; 290:304-310), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto, *et al.*, Cell, 1980; 22:787-797), the herpes thymidine kinase promoter (Wagner *et al.*,

Proc. Natl. Acad. Sci. U.S.A., 1981; 78:1441-1445), the regulatory sequences of the metallothionein gene (Brinster *et al.*, Nature, 1982; 296:39-42, prokaryotic expression vectors such as the β-lactamase promoter (Villa-Komaroff, *et al.*, Proc. Natl. Acad. Sci. U.S.A. 1978; 75:3727-3731), or the tac promoter (DeBoer, *et al.*, Proc. Natl.

5   Acad. Sci. U.S.A. 1983; 80:21-25) (see also "Useful proteins from recombinant bacteria" in Scientific American, 1980, 242:74-94), promoter elements from yeast or other fungi such as the Gal 4 promoter, the ADC (alcohol dehydrogenase) promoter, PGK (phosphoglycerol kinase) promoter, alkaline phosphatase promoter, and transcriptional control regions that exhibit tissue specificity, such as, *e.g.*, endothelial

10   cell-specific promoters.

        Solubilized forms of the protein can be obtained where necessary by solubilizing inclusion bodies or reconstituting membrane components, *e.g.*, by treatment with detergent, and if desired sonication or other mechanical processes, as described above. The solubilized protein can be isolated using various techniques,

15   such as polyacrylamide gel electrophoresis (PAGE), isoelectric focusing, 2-dimensional gel electrophoresis, chromatography (*e.g.*, ion exchange, affinity, immunoaffinity, and sizing column chromatography), centrifugation, differential solubility, immunoprecipitation, by any other standard technique for the purification of proteins, or by a combination of such techniques.

20   Since β-subunits 1-3 are known to bind the α-subunits of sodium channels, the present invention also contemplates co-expression of a β-subunit with NaIII18. While the role played by β-subunits in determining the pharmacological properties of voltage-gated sodium channels appears to be minor, at least for the commonly-studied binding sites, the β-subunits do appear to have effects on the

25   biophysics (gating kinetics) of sodium channel function. Therefore, to the extent that biophysics and drug interactions are linked, the β-subunits may affect pharmacology of agents used to modulate sodium channel activity. Some known β-subunits that may be co-expressed with the NaIII18 subunit of the invention are described in Isom et al., Neuron 1994; 12:1183-94; International PCT publication WO 01/44293 to Plumpton

30   et al.; International PCT publication WO 01/23570 to d'Andrea et al.; U.S. published patent application 2002/0045229 to Qin et al.; and under GenBank Accession Nos.

U87445, AF007783, AH005825, AF007783, AF04948, L10338 and L16242, among others

hNaIII18 Binding Partners

5   The present invention further provides a method for identifying physiological binding partners of hNaIII18. One method for evaluating and identifying hNaIII18 binding partners is the yeast two-hybrid screen. Preferably, the yeast two-hybrid screen is performed using an cell library with yeast that are transformed with recombinant hNaIII18. Alternatively, hNaIII18 can be used as a

10   capture or affinity purification reagent. In another alternative, labeled hNaIII18 can be used as a probe for binding, *e.g.*, by immunoprecipitation or Western analysis. Several expected hNaIII18 binding partners are the sodium channel β subunits, as described in the section above.

       Generally, binding interactions between hNaIII18 and any of its

15   binding partners will be strongest under conditions approximating those found in the native cell, *i.e.*, physiological conditions of ionic strength, pH and temperature, and particularly those obtaining in the cell membrane. Perturbation of these conditions will tend to disrupt the stability of a binding interaction.

20   ### *Antibodies to hNaIII18*

       Antibodies to hNaIII18 are useful, *inter alia*, for determining the presence of hNaIII18 in a cell and for cellular regulation (*i.e.*, inhibition) of hNaIII18 activity, as set forth below. According to the invention, a hNaIII18 polypeptide produced recombinantly or by chemical synthesis, and fragments or other derivatives

25   or analogs thereof, including fusion proteins, may be used as immunogens to generate antibodies that recognize the hNaIII18 polypeptide. Such antibodies include but are not limited to polyclonal, monoclonal, chimeric, single chain, Fab fragments, and Fab expression libraries. Such an antibody binds specifically to hNaIII18, and may recognize either a mutant form of hNaIII18 or wild-type hNaIII18, or both. The

30   antibodies of the present invention are specific for hNaIII18 and either do not recognize, or bind with lower affinity to, orthologs of hNaIII18. In one embodiment,

specific binding of such antibodies to hNaIII18 polypeptides provides the ability to detect the presence of the hNaIII18 polypeptide in a sample. In another embodiment, specific binding of such antibodies to hNaIII18 polypeptides provides the ability to preferentially inhibit the activity of hNaIII18, or an ion channel comprising hNaIII18.

5   Various procedures known in the art may be used for the production of antibodies against hNaIII18 polypeptides. These include but are not limited to the hybridoma technique originally developed by Kohler and Milstein (Nature 1975; 256:495-497), as well as the trioma technique, the human B-cell hybridoma technique (Kozbor *et al.*, Immunology Today 1983, 4:72; Cote *et al.*, Proc. Natl. Acad. Sci.

10   1983, 80:2026-2030), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole *et al.*, in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., 1985, pp. 77-96).

hNaIII18 Agonists and Antagonists

15   The present invention also contemplates the identification of compounds that modulate hNaIII18 sodium channel activation and activity. Such compounds are useful, *e.g.*, for inhibiting (*i.e.*, antagonizing) or increasing (*i.e.*, agonizing) biological activities that are associated with sodium channel activation and/or as therapeutic agents for treating disorders associated with excessive sodium

20   channel activation.

Compounds that modulate hNaIII18 activity or an activity associated therewith may be readily identified using screening methods of the present invention. In one embodiment, compounds identified by the screening methods of this invention bind to a hNaIII18-subunit containing ion channel. Compounds identified by the

25   present method may antagonize or agonize hNaIII18 subunit-containing channel activity, as well as a related downstream biological effect (*e.g.*, the ability of DRG to transmit nociceptive signals from the PNS to the CNS) that are associated with excessive sodium channel current and activity.

In vivo or cell culture assays may be used to determine whether a test

30   compound functions as an antagonist to inhibit hNaIII18 activity in cells. For instance, cell culture assays may be used to measure a test compound's ability to modulate an activity, such as induction, strength or duration of sodium channel

current associated with hNaIII18 subunit-containing sodium channel activity. Such

assays generally comprise contacting a cell that expresses a hNaIII18 subunit

containing sodium channel with a test compound. The cell should preferably be

contacted with the test compound before or during exposure to an agent or stimulus

5   that otherwise would serve to depolarize the cell membrane and thus activate (*i.e.*,

open) the sodium channel: *e.g.* a high potassium chloride saline solution, or an

extracellular field-stimulating electrode. The cell can then be examined to determine

whether a response otherwise associated with sodium channel activation has been

inhibited. In a non-limiting embodiment, the response of the cell treated with the test

10   compound is compared to that of a control cell that has not been treated with the test

compound. Cell assays include those utilizing conventional, electrode-based,

electrophysiological techniques, as well as the new generation high-throughput,

planar electrode (orifice) -based, electrophysiological technologies, among others.

Other assays include monitoring changes in membrane potential with appropriate

15   fluorescent, or luminescent, dyes, measuring ion flux through the sodium channel

with a radiolabeled tracer, or assaying downstream consequences of sodium channel

activation, such as calcium mobilization or effects on gene expression, using an

appropriate reporter system.

Positive modulation (*i.e.*, agonism) of hNaIII18 subunit-containing

20   channels may be desirable under certain circumstances, and screening for such

agonists can be conducted according to the methods of the invention.

Screening

According to the present invention, nucleotide sequences encoding

25   hNaIII18 are useful targets to identify drugs that are effective in preventing or

alleviating pain, or drugs that can be used as anti-epileptics/anticonvulsants,

anesthetic antiarrythmics, and in the treatment of bipolar disorder (see section

entitled Therapeutics, below), any of which may be associated with the function of the

sodium channel. Examples of such drugs include without limitation: (i) isolated

30   nucleic acids capable of altering expression of hNaIII18 (*e.g.,* antisense or ribozyme

molecules); (ii) small organic molecules that bind to and modulate the function of a

hNaIII18 subunit or a hNaIII18 subunit-containing ion channel; and (iii) peptides or

peptide analogs that bind to and modulate the function of a hNaIII18 subunit or a hNaIII18 subunit-containing ion channel. In addition, the nucleotide sequences encoding hNaIII18 are useful for studying the role of the channels both in pain perception and in physiological and pathological brain functions.

5   Any screening technique known in the art can be used to screen for agonists or antagonists. The present invention contemplates screens for small molecules and mimics, as well as screens for natural products that bind to and agonize or antagonize hNaIII18-containing ion channels. For example, natural product libraries can be screened using assays of the invention for molecules that agonize or

10   antagonize hNaIII18-containing ion channel activity.

Knowledge of the primary sequence of hNaIII18, and the similarity of that sequence with proteins of known function, can provide an initial lead to inhibitors or antagonists. Identification and screening of modulators is further facilitated by determining structural features of the protein, e.g., using X-ray crystallography,

15   neutron diffraction, nuclear magnetic resonance spectrometry, and other techniques for structure determination. These techniques provide for the rational design or identification of agonists and antagonists.

Another approach uses recombinant bacteriophage to produce large libraries. Using the "phage method" (Scott and Smith, Science 1990, 249:386-390;

20   Cwirla, et al., Proc. Natl. Acad. Sci. USA 1990, 87:6378-6382; Devlin et al., Science 1990, 49:404-406), very large libraries can be constructed (106-108 chemical entities). A second approach uses primarily chemical methods, of which the Geysen method (Geysen et al., Molecular Immunology 1986, 23:709-715; Geysen et al. J. Immunologic Methods 1987, 102:259-274); and the method of Fodor et al. (Science

25   1991, 251:767-773) are examples. Furka et al. (14th International Congress of Biochemistry 1988, Volume #5, Abstract FR:013; Furka, Int. J. Peptide Protein Res. 1991, 37:487-493), Houghton (U.S. Patent No. 4,631,211) and Rutter et al. (U.S. Patent No. 5,010,175) generally describe methods to produce a mixture of peptides that can be tested as agonists or antagonists.

30   In another aspect, synthetic libraries, such as those described in Needels et al., Proc. Natl. Acad. Sci. USA 1993, 90:10700-4; Ohlmeyer et al., Proc. Natl. Acad. Sci. USA 1993, 90:10922-10926; Lam et al., PCT Publication No. WO

92/00252; and Kocis et al., PCT Publication No. WO 9428028, and the like, can be adapted to screen for compounds according to the present invention.

Test compounds can be screened from large libraries of synthetic or natural compounds. Numerous means are currently used for random and directed synthesis of saccharide, peptide, and nucleic acid based compounds. Synthetic compound libraries are commercially available from a variety of sources, including Maybridge Chemical Co. (Trevillet, Cornwall, UK), Comgenex (Princeton, NJ), Brandon Associates (Merrimack, NH), and Microsource (New Milford, CT). A rare chemical library is available from Aldrich (Milwaukee, WI). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available from a variety of sources including, *e.g.,* Pan Laboratories (Bothell, WA) and MycoSearch (NC), or are readily producible de novo. Additionally, natural and synthetically produced libraries and compounds are readily modified through conventional chemical, physical, and biochemical means (see, *e.g.,* Blondelle et al., TIBTech 1996, 14:60).

In Vitro *Screening Methods and Activity Assays*
Cell-based screening

Intact cells expressing a hNaIII18 subunit-containing ion channel can be used in screening methods to identify candidate compounds useful in modulating the activity of sodium channels containing hNaIII18. In one embodiment, a cell line is established that stably expresses or overexpresses the hNaIII18 subunit protein, either alone or in combination with one or more other sodium channel β subunits, to form a functional sodium channel. Alternatively, cells (including without limitation mammalian, invertebrate, yeast, or bacterial cells) are transiently programmed to express a hNaIII18 subunit protein by introduction of the appropriate DNA or mRNA. Identification of candidate compounds can be achieved using any suitable assay, including without limitation: (i) assays that measure binding of test compounds to hNaIII18 (alone or in combination with sodium channel β subunits described *supra*): (ii) assays that measure the ability of a test compound to modulate (*i.e.,* agonize or antagonize) a measurable activity or function of hNaIII18 or a hNaIII18 subunit-containing ion channel; and (iii) assays that measure the ability of a compound to

enhance or inhibit the transcriptional activity of sequences derived from the promoter (*i.e.*, regulatory) regions of the hNaIII18 gene.

Any cell assay system that allows for assessment of functional activity of a hNaIII18 subunit-containing sodium channel is encompassed by the present

5   invention. In a specific embodiment, described *infra*, the assay can be used to identify compounds that selectively modulate the hNaIII18 subunit protein, which can be determined by assessing the effects on NaIII18 subunit-expressing cells contacted with a test compound. The assay system can thus be used to identify compounds that selectively produce a functional effect through hNaIII18 sodium channels.

10   Compounds that decrease activity of the sodium channel in response to activation may be useful as novel therapeutics in the amelioration of neuropathic pain mediated by DRG neurons, or as anti-epileptics/convulsants, anesthetics, antiarrythmics, or in the treatment of bipolar disorder.

Compounds that increase activity of sodium channels may be useful as

15   cognitive enhancers, or in disorders such schizophrenia. In these instances, a subtype-selective agent would be preferable to offset the potential for proconvulsant effects and to increase cardiac contractility in individuals suffering from heart failure.

Alternatively, the change in membrane potential induced by sodium ions of the voltage-gated channel-containing cells may be monitored using

20   fluorescence methods. When using fluorescence methods, the voltage-gated channel containing cells may be incubated with a membrane potential indicating agent that allows for a determination of changes in the membrane potential of the cells caused by the influx of sodium ions. Such membrane potential indicating agents include fluorescent indicators, such as those provided in a Molecular Devices Membrane

25   Potential Kits for the FLIPR/Flexstation, DIBAC4(3), DiOC6(6) DiOC5(3), DiOC2(3) and fluorescence resonance energy transfer (FRET) based dyes such as JC1, and JC9, among others.

Another method that allows for assessment of functional activity of hNaIII18-containing sodium channels involves monitoring the change in membrane

30   potential induced by sodium ions on the channel-containing cells by fluorescent methods, *e.g.*, using a FLIPR assay (Fluorescence Image Plate Reader; available from Molecular Devices)(Rose et al. Pflugers Arch. 1999 Dec;439(1-2):201-7). Another

method involves radioactive flux assays that measure the ability of radioactive tracer ions such as [^{22}Na] and [^{14}C] guanidinium to pass into the cell upon channel activation (Barann M. et al. Naunyn Schmiedebergs Arch Pharmacol. 1999; 360(3):234-41). After the channel is activated, concentrations of these tracer ions increase inside the

5   cell. Free extra-cellular tracer is washed away, cells are lysed, and radioactivity in the lysates is counted using standard scintillation counters or other radioactivity analysis instruments.

Yet another method involves measuring cell viability upon veratridine-mediated stabilization of sodium channels in their open conformation (Okuyama K. et

10   al., Eur J Pharmacol. 2000; 398(2):209-16). Cells undergo toxic sodium overload followed by cell death. Compounds that prevent cell death, or cellular toxicity, can be assayed with standard cytoxicity kits and with standard cell viability dyes such as alamar blue.

15   <div align="center">**Cell-Free Screening**</div>

In another embodiment, an assay is a cell-free assay comprising contacting a hNaIII18 polypeptide or biologically active portion thereof with a test compound and determining the ability of the test compound to modulate (*e.g.,* stimulate or inhibit) the activity of the hNaIII18 polypeptide or biologically active

20   portion thereof.

In yet another embodiment, the cell-free assay comprises (i) contacting the hNaIII18 polypeptide of the invention or biologically active portion thereof with a known compound or polypeptide which binds the hNaIII18 polypeptide to form an assay complex; (ii) contacting the assay complex with a test compound; (iii)

25   determining the ability of the test compound to interact with the hNaIII18 polypeptide by determining the ability of the test compound to modulate the effect of the known compound on the activity of the sodium channel.

More specifically, a cell-free method can involve monitoring the specific binding of a radiolabeled sodium channel selective neurotoxin, such as

30   [^{3}H]tetrodotoxin or [^{3}H]batrachotoxin, or a high affinity small-molecule ligand, to a membrane preparation from cells or tissues engineered to express hNaIII18-containing sodium channels (Garritsen A. et al. Eur J Pharmacol. 1988; 145(3):261-6;

MacKinnon AC. et al. J Pharmacol. 1995; 115(6):1103-9; Bambrick L. et al., J Pharmacol Toxicol Methods. 1994; 32(3):129-38). Following techniques that are well know in the art, total binding to membranes can be measured upon incubation with the radioligand until the biomolecular reaction reaches equilibrium. Nonspecific

5   binding is defined in the presence of an unlabelled competitor ligand. Specific binding is the subtraction of total minus nonspecific binding. Compounds that modulate specific binding can thereby be identified.

In another embodiment, modulators of expression of the hNaIII18 polypeptide of the invention are identified in a method in which a cell is contacted

10   with a candidate compound and the expression of the mRNA or protein corresponding to hNaIII18 in the cell is determined. The level of expression of the hNaIII18 mRNA or protein in the presence of the candidate compound is compared to the level of expression of the hNaIII18 mRNA or protein in the absence of the candidate compound. The candidate compound can thereby be identified as a modulator of

15   expression of the hNaIII18 polypeptide of the invention based on this comparison. For example, when expression of the hNaIII18 mRNA or protein is increased in the presence of the candidate compound compared to in the absence of the candidate compound, then the candidate compound is identified as a stimulator of hNaIII18 mRNA or protein expression. Alternatively, when expression of the hNaIII18 mRNA

20   or protein is specifically reduced in the presence of the candidate compound compared to in the absence of the candidate compound, then the candidate compound is identified as an inhibitor of hNaIII18 mRNA or protein expression. In view of this disclosure, the level of the hNaIII18 mRNA or protein expression in cells can be determined by methods known in the art.

25

High-Throughput Screen

Drug candidates according to the invention can be identified by screening in high-throughput assays, including without limitation cell-based or cell-free assays. It will be appreciated by those skilled in the art that different types of

30   assays can be used to detect different types of drug candidates. Several methods of automated assays have been developed in recent years so as to permit screening of tens of thousands of compounds in a short period of time. Such high-throughput

screening methods are particularly preferred. The use of high-throughput screening
assays to test for agents is greatly facilitated by the availability of the large amounts
of purified hNaIII18 polypeptides provided by the invention.

5

<p style="text-align:center"><u>Therapeutic Uses</u></p>

It is desirable to modulate the function of sodium channels in a number
of clinical and therapeutic environments. Sodium channels are implicated in
conditions including chronic and neuropathic pain, cardiac arrhythmias (Duch et al.,
Toxicol Lett 1998; 100-101:255-63), neuronal disorders associated with deficient

10   oxygen supply or mitochondrial dysfunction (Urenjak et al., Amino Acids 1998;14(1-
3):151-8), and epilepsy (Ragsdale et al., Brain Res Rev 1998;26(1):16-28). In
addition, inhibition of sodium channels is an effect of local anesthetics (Li et al., Mol
Pharmacol 1999; 55(1):134-41).

According to the present invention, inhibition of hNaIII18 subunit-

15   containing sodium channel activity may be used as a treatment option in patients with
a pain disorder, such as but not limited to a neuropathic pain-related disease such as,
e.g., pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus,
causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic
pain is also caused by nerve damage from chronic alcoholism, human

20   immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies.
The neuronal hyperexcitability and corresponding molecular changes in neuropathic
pain have many features in common with the cellular changes in certain forms of
epilepsy. This has led to the use of anticonvulsant drugs for the treatment of
neuropathic pain (Jensen, Eur J Pain 2002;6 Suppl A:61-8). Local anesthetics such as

25   lidocaine and mexiletine have also be shown to inhibit TTX-S sodium channel
activity in hyperexcitable neurons in rat (Novartis Found Symp 2002;241:189-201;
discussion 202-5, 226-32).

Inhibition of the sodium channel of the present invention may also be
used as a treatment option in patients with chronic pain. In chronic pain, the pain can

30   be mediated by multiple mechanisms. This type of pain generally arises from injury
to the peripheral or central nervous tissue. The chronic pain-type syndromes include
pain associated with spinal cord injury, multiple sclerosis, post-herpetic neuralgia,

trigeminal neuralgia, phantom pain, causalgia, and reflex sympathetic dystrophy and lower back pain.

Inhibition of the sodium channel of the present invention may also be used as a treatment option in patients with nociceptive pain.

5

Inhibition of Protein Synthesis or Sodium Channel Activity

Gene transcription and protein translation may be inhibited by administration of exogenous compounds. Exogenous compounds may interact with extracellular and/or intracellular messenger systems to regulate protein synthesis. In this embodiment, exogenous compounds that inhibit hNaIII18 protein synthesis may be used in the prevention and/or treatment for pain resulting from persistent channel activity.

Accordingly, in an exemplary embodiment, the modulatory method of the invention involves contacting a cell, tissue or subject with an agent that modulates one or more of the activities of hNaIII18 protein activity associated with the cell. An agent that modulates hNaIII18 protein activity can be an agent as described herein, such as a nucleic acid or a protein, an hNaIII18-specific antibody, an hNaIII18 agonist or antagonist, a peptidomimetic of an hNaIII8 agonist or antagonist, or other small molecule. In one embodiment, the agent stimulates one or more hNaIII18 activities. In another embodiment the agent inhibits one or more hNaIII18 activities. Examples of such inhibitory agents include antisense hNaIII18 nucleic acid molecules, anti-hNaIII18 antibodies, and hNaIII18 inhibitors. These modulatory methods can be performed *in vitro* (*e.g.*, by culturing the cell with the agent) or, alternatively, *in vivo* (*e.g.*, by administering the agent to a subject). As such, the present invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant or unwanted expression or activity of a hNaIII18 protein or nucleic acid molecule. In one embodiment, the method involves administering an agent (*e.g.*, an agent identified by a screening assay described herein), or combination of agents that downregulates hNaIII18 expression or activity or the activity of a hNaIII18 subunit-containing ion channel.

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In yet another embodiment, the agent enhances one or more hNaIII18 activities, such as by administering a hNaIII18 protein or nucleic acid molecule as therapy to compensate for reduced or aberrant hNaIII18 expression or activity.

The present invention further provides antisense nucleic acids, which may be used to inhibit expression of hNaIII18 nucleotide sequences of the invention. This antisense technology has been described as inhibiting the peripheral tetrodotoxin (TTX)-resistant sodium channel, NaV1.8, found in sensory neurons, when administered intrathecally (Lai et al., Pain 2002; 95 (1-2):143-52). According to this method, the antisense nucleic acid, upon hybridizing under cytoplasmic conditions with complementary bases in an RNA or DNA molecule, inhibits the RNA or DNA. Additionally, hybridization of the antisense nucleic acid to the DNA or RNA may inhibit transcription of the DNA into RNA and/or translation of the RNA into the protein. If the RNA is a messenger RNA transcript, the antisense nucleic acid is a counter-transcript or mRNA-interfering complementary nucleic acid. Antisense nucleic acid molecules can be encoded by a recombinant gene for expression in a cell (see, e.g., U.S. Patent No. 5,814,500; U.S. Patent No. 5,811,234) or can be prepared synthetically (e.g., U.S. Patent No. 5,780,607).

Alternatively, antibody molecules or antigen-binding antibody fragments can be administered either directly or by expressing nucleotide sequences encoding antibodies or binding fragments thereof within the target cell population by utilizing, for example, techniques such as those described in Marasco et al. (Proc. Natl. Acad Sci. USA, 1993, 90:7889-7893).

Formulations and Administration

The drug candidate or agent that modulates hNaIII18 activity is advantageously formulated in a pharmaceutical composition by admixing the drug candidate or agent with a pharmaceutically acceptable carrier. This agent may then be designated as the active ingredient, or therapeutic agent for use, for example, against chronic, neuropathic pain, or nociceptive pain

The form, amount and route of administration of the therapeutic compound envisioned for use depends on the type and severity of the disease or condition to be treated, as well as the patient's state of health, gender, weight, age,

etc., and can be determined by an attending medical practitioner in view, *e.g.*, of the results of published clinical trials. The concentration or amount of the active ingredient depends on the desired dosage and administration regimen, as discussed below. Suitable dose ranges may include from about 1 mg/kg to about 100 mg/kg of body weight per day.

The pharmaceutical compositions may also include other biologically active substances in combination with the NaIII18 modulatory agent. Such substances include but are not limited to opioids such as morphine, codeine, fentynyl, oxycodone, hydrocodone, and buprenorphine; and non-steroidal anti-inflammatory drugs (NSAID's) such as but not limited to ibuprofen and COX-2 inhibitors, among others

The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to a human. Preferably, as used herein, the term "pharmaceutically acceptable" means that the carrier has been approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the active ingredient is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or aqueous solution saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

According to the invention, the pharmaceutical composition of the invention can be introduced parenterally, transmucosally, *e.g.*, orally (per os), nasally, rectally, or transdermally. Parental routes include intravenous, intra-arteriole, intramuscular, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial administration. The pharmaceutical composition may alternatively be

adapted for topical or transdermal application, such in a salve, cream, lotion, spray or transdermal patch system.

The pharmaceutical compositions may be added to a retained physiological fluid such as blood or synovial fluid. For CNS (Central Nervous

5   System) administration, a variety of techniques are available for promoting transfer of the therapeutic across the blood brain barrier including disruption by surgery or injection, co-administration of drugs that transiently open adhesion contact between CNS vasculature endothelial cells, and co-administration of substances that facilitate translocation through such cells.

10   In another embodiment, the active ingredient can be delivered in a vesicle, in particular a liposome (see Langer, Science 1990; 249:1527-1533; Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss: New York 1989 pp. 353-365; Lopez-Berestein, ibid., pp. 317-327; see generally ibid.).

15   In yet another embodiment, the therapeutic substance can be delivered in a controlled release formulation. For example, an active ingredient may be administered using intravenous infusion with a continuous pump, in a polymer matrix such as poly-lactic/glutamic acid (PLGA), a pellet containing a mixture of cholesterol and the active ingredient (SilasticRTM; Dow Corning, Midland, MI; see U.S. Patent

20   No. 5,554,601) implanted subcutaneously, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration.

Compounds identified in the screening methods described herein (i.e., modulators of sodium channel activity), may be provided to the patient in formulations that are known in the art and may include any pharmaceutically

25   acceptable additives, such as excipients, lubricants, diluents, flavorants, colorants, and disintegrants. The formulations may be produced in useful dosage units such as tablet, caplet, capsule, liquid, or injection. In a further embodiment, these compounds are also administered in conjunction with other therapeutic agents such as the local anesthetics and anti-epileptic or anti-convulsants discussed supra.

30   The form and amount of therapeutic compound envisioned for use depends on the type of disease and the severity of the desired effect, patient state, etc., and can be determined by one skilled in the art.

EXAMPLES

The present invention is also described by means of an example,
presented below. The use of such an example is illustrative only and in no way limits
5   the scope and meaning of the invention or of any exemplified term. Likewise, the
invention is not limited to any particular preferred embodiments described herein.
Indeed, many modifications and variations of the invention will be apparent to those
skilled in the art upon reading this specification and can be made without departing
from its spirit and scope. The invention is therefore encompassed by the appended
10   claims along with the full scope of equivalents to which the claims are entitled.

EXAMPLE 1:   **CLONING AND EXPRESSION OF HUMAN NaIII18**

Methods

Reverse transcription and amplification of hNaIII18 cDNA. Reverse
15   transcription was carried out using ThermoScript Reverse Transcriptase (Life
Technologies, Rockville, MD), at an annealing temperature of 55°C to maximize the
likelihood of obtaining a full-length mRNA, according to manufacturer's instructions.

The following primers were designed to amplify the resulting full-
length hNaIII18 cDNA:

forward primer (SEQ ID NO: 7)	5' - ATAAGAATGCGGCCGCTGAAAAGATGGCACAGGCAC-3'
reverse primer (SEQ ID NO: 8)	5' - ATAGTTTAGCGGCCGCCTTGAAGTCCAGTTGACACA -3'

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Primers were designed from the human NaIII (SCN3A) mRNA
sequence previously identified (GenBank Accession # AJ251507).

Full-length cDNA (6000 base-pairs) was amplified using the Expand
Long Template PCR (Boehringer Mannheim, Indianapolis, IA) according to the
25   manufacturer's instructions. This enzyme is a mixture of thermostable Taq and Pwo

DNA polymerases. The number of cycles used for amplification was decreased to 28 cycles instead of the traditional 30-35 as an added precaution to minimize the occurrence of mutations during PCR.

Purification and cloning of PCR products into expression vectors.

5   PCR products resulting from the above-described reaction were visualized after electrophoresis on an agarose gel containing Crystal Violet. DNA was purified from the gel using methods well known in the art. DNA was stored in Tris-EDTA buffer, pH 7.4.

The PCR-amplified cDNA was cloned into a low-copy number

10   expression vector, pLCTM1 (kindly provided by Al Goldin, UCI) according to standard procedures. This vector is under the control of the origin of replication (ORI) from plasmid pACYC184, which has a limited number of replication cycles, resulting in a decreased error rate during DNA replication.

Further, the plasmid contains a tetracycline-resistance gene instead of

15   an ampicillin-resistance gene for selection. Tetracycline is less likely to induce mutations than ampicillin during selection. The plasmid also contains a neomycin resistant gene (NeoR) for selection of stable cell lines using the neomycin analog G418.

Once cloned, the vectors were transformed into maximum efficiency

20   STBL2 competent *E. coli* bacteria (Life Technologies, Rockville, MD), provided in the kit according to manufacturer's instructions. These cells optimize the cloning of unstable inserts. Bacteria expressing hNaIII18 were grown at 30-33°C, and maintained in exponential (log) growth phase for the duration of culture.

Small tetracycline-resistant colonies were selected and grown-up for

25   small-scale DNA preparations and large-scale preparations. The concentration of tetracycline was kept low (15 μg/ml) to further minimize adverse growth conditions. The cDNA was extracted using the Wizard Plus SV Minipreps DNA Purification System Kit (Promega, Madison, WI) according to the manufacturer's instructions, or Qiagen Midipreps according to manufacturer's instructions (Qiagen, Valencia, CA).

30   cDNA was then analyzed by restriction digest, and partial sequencing. Full sequencing was performed by MWG (North Carolina). Partial sequencing was done with standard DTCS sequencing method using a commercial Beckman Coulter kit.

Transient and stable transfection. In order to identify functional
clones, human embryonic kidney cells (HEK293) were transiently transfected with
clones that were identified as having the correct insert, and surveyed by an
electrophysiological assay (Fugene transfection reagent, according to manufacturer's
recommendation). One clone, pLCTM1huNaIII-18, was determined to be functional
as it gave large TTX-S currents with the expected activation and inactivation kinetics
typical of NaIII channel. For example, typical activation is measured within fractions
of ms at Vm=0mV (corresponding Imax). Inactivation is measured as the time
constant between 1-3 ms at Vm=0mV (increasing to 20 ms at -50 mV to 0.5 ms at
+40mV). Recovery from inactivation is a time constant of about 10ms at Vm=-
100mV and 60 ms at -80mV (see *e.g.,* Cummins et al., J Neurosci 2001; 21:52-
5961).

This clone was fully sequenced for confirmation. In addition, several
non-functional clones were partially sequenced.

Clone pLLCTM1huNaIII-18 was used to generate a stable cell line in
HEK293 cells. Fugene-mediated transfection of HEK cells was performed in 35 mm
dish followed by G418 selection (300 and 500 µg/ml), colony isolation, line
expansion. G418-resistant cells were then analyzed with immunocytochemistry, RT-
PCR and electrophysiology according to standard techniques.

Electrophysiology. Stably transfected cells were grown on poly DL-
lysine-coated glass coverslips at ~2,000 cells/slip, or Petri dishes at ~10,000 cells/dish
and were then placed into the electrophysiology recording chamber and infused with
an extracellular solution (140 mM NaCl, 4.7 mM KCl, 1.2 mM MgCl$_2$, 1 mM CaCl$_2$,
11 mM glucose and 5 mM HEPES, pH 7.4) at a rate of 2 ml/min. Electrodes were
prepared by pulling Patch pipettes (borosilicate glass) using a Sutter P-97 electrode
puller, and were filled with a solution containing 110 mM CsCl, 10 mM NaCl, 5 mM
MgCl$_2$, 11 mM EGTA, 10 mM HEPES, 2 mM ATP and 1 mM GTP, pH 7.25,
osmolarity 275-290 mOsm. When filled with this solution, the electrodes had
resistances of about 1-4 MS. Currents were recorded using a whole-cell voltage
clamp techniques as described in Hamill et al. (Pflugers Arch. 1981; 391; 85-100), at
room temperature (21-23 °C). Briefly, currents were recorded using an Axopatch
200A amplifier (Axon Instruments, Foster City, CA) and were leak-subtracted (P/4),

low-pass filtered (3 kHz, 8-pole Bessel), digitized (20-50-μs intervals), and stored

using Digidata 1200 B interface and Pclamp6/Clampex software (Axon Instruments,

Foster City, CA). Residual series access resistance was largely (75-80%) canceled

using built-in amplifier circuitry. The junction potential calculated using JPCalcW

5   software (Cell MicroControl, Virginia Beach, VA) was small (<7 mV); so, no

correction of the holding voltage was made.

        To take I-V curves, cells were held at a holding voltage, V_h = -90mV.

A series of 16 depolarizing pulses (10ms in duration) incrementing in 10 mV steps

were applied at a frequency of 0.5 Hz. The peak values of currents were plotted

10   against corresponding voltage steps to get the I-V curve. From this plot V_{max}, *i.e.*, the

voltage causing the maximal Na$^+$ current, as well as rising times to peak and time

constant for inactivation at different voltages were determined. To get steady-state

inactivation curves, cells were held at a holding voltage, V_h = -120mV to remove

residual inactivation. A series of 30 depolarizing conditioning pre-pulses (each

15   100ms in duration) incrementing in 5 mV steps immediately followed by a 5 ms

testing pulse, V_t, to V_{max} were applied at a frequency of 0.5 Hz. The peak currents in

response to V_t were plotted against the size of corresponding conditioning pre-pulses,

V_c, to get steady-state inactivation curve. The Boltzman fit to this curve, *i.e.*,

$\{1/[1+\exp((V+ V\frac{1}{2}) /k)]\}$, returned the values of V½ (the half-inactivation voltage)

20   and k (the slope of the curve).

        To measure recovery from inactivation, cells were held at a holding

voltage

V_h = -120mV to remove residual steady-state inactivation. The depolarizing

conditioning pre-pulse (100 ms in duration) was applied to V_c to cause complete

25   inactivation of the channels (usually V_c=-10 mV) . The conditioning pre-pulse was

immediately followed by hyperpolarizing gap back to -120mV of a variable duration.

The gap duration was incremented in subsequent cycles in varying steps (2 ms -100

ms) depending on the speed of recovery. The gap was immediately followed by the

testing pulse V_t (10 ms in length) to assess the fraction of Na$^+$ channels available for

30   activation. The cycle was repeated every 5 seconds while the gap duration was

incremented. The peak currents to V_t were plotted against the corresponding gap

duration to get the kinetics of recovery. The mono- or double- exponential fit to the data returned the time constant, $\tau_{repr.}$, of repriming from inactivation.

Results

5   **Identification of a splice-variant for human NaIII (SCN3).** Clone pLCM1huNaIII-18 is a novel splice variant and contains an additional 147 nucleotides corresponding to 49 amino acids in the cytoplasmic loop between domain 1S6 and IIS1 (see SEQ ID NO: 1 and SEQ ID NO: 2). Partial sequencing of several other clones that were not determined to have functional activity revealed sequences

10   that either matched the published sequence (GenBank Accession #AJ251507) or contained an extra 9 or 96 nucleotides. The shorter splicing patterns correspond to what had been described for the rat NaIII clone (Schaller et al., *J Neurosci* 1992; 12(4):1370-81), resulting in a protein with an additional 3 (rNaIIIa) or 22 (rNaIIIb) amino acids, but had not been described for the human NaIII before.

15   Subsequent to the completion of the cloning of hNaIII18, it was discovered that a clone having the same 147 nucleotide insert was deposited in GenBank on February 1, 2001 (GenBank Accession # AF225986-SEQ ID NO: 5). See cDNA alignment in Figure 8. However, that encoded amino acid sequence differs from the sequence disclosed herein by 12 amino acids (between two clones), at

20   amino acid residues 208, 475, 495, 508, 604,1163, 1576, 1614, 1741, 1743, 1862 and 1966, respectively (SEQ ID NO: 2 vs. SEQ ID NO: 6). See amino acid aligment of Figure 9.

Stable transfection of the pLCM1huNaIII-18 resulted in the generation of two cell lines that expressed the expected ~220 kDa hNaIII18 protein and

25   exhibited functional sodium channels, designated 293/huNaIII18-300-20 and 293/huNaIII18-500-35, with appropriate TTX-S currents. 293/huNaIII18-300-20 had an activation threshold voltage of -40 mV (Figure 9A), a steady state V ½ inactivation voltage of -58 mV (Figure 9B), a recovery time after inactivation of 2.5 ms (fast component) AND 113 ms (slow component-(Figure 9C), and inactivation kinetics of

30   0.8 ms (Figure 9D).

****

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

Patents, patent applications, publications, procedures, and the like are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid comprising a nucleotide sequence encoding a polypeptide

having the amino acid sequence of Figure 2 (SEQ ID NO: 2).

2. The isolated nucleic acid of claim 1, comprising the nucleotide sequence of Figure 1 (SEQ ID NO: 1).

3. A recombinant vector comprising a nucleotide sequence encoding a polypeptide having the amino acid sequence of Figure 2 (SEQ ID NO:2).

4. A host cell comprising the recombinant vector of claim 3.

5. A host cell genetically engineered to comprise the nucleic acid of claim 1.

6. The host cell of claim 5 which is eukaryotic.

7. A eukaryotic host cell genetically engineered to express, or overexpress, a polypeptide having the amino acid sequence of Figure 2 (SEQ ID NO: 2).

8. A method for expressing a polypeptide in a cell cultured *in vitro* comprising culturing the cell of claim 4, 5, 6 or 7 under conditions conducive to the expression of the polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2).

9. An isolated polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2).

10. A host cell genetically engineered to co-express a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2) and a β-subunit of a sodium channel selected from the group consisting of $\beta 1$, $\beta 2$, and $\beta 3$.

11. An antibody or antigen-binding fragment that specifically binds to a polypeptide having the amino acid sequence of Figure 2 (SEQ ID NO: 2).

12. The antibody of claim 11, which is a monoclonal antibody.

13. A method for detecting expression in a sample of a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2), which method comprises detecting specific binding of the antibody or antigen-binding fragment of claim 11 to a polypeptide in the sample.

14. A method for identifying a test compound that binds to a sodium channel comprising a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2), which method comprises:

    (i) contacting a host cell that expresses a sodium channel comprising a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2) with a test compound; and

    (ii) determining whether the test compound binds to the host cell but not to a control cell that does not express a sodium channel comprising a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2).

15. An assay method for identifying a test compound that modulates the activity of a sodium channel comprising a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2), which method comprises:

    (i) providing a host cell that expresses a functional sodium channel comprising at least one polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2),

    (ii) contacting the host cell with a test compound under conditions that would activate sodium channel activity of said functional sodium channel in the absence of

the test compound; and

(iii) determining whether the host cell contacted with the test compound exhibits a modulation in activity of the functional sodium channel.

16. The assay method of claim 15, wherein the host cell has been genetically engineered to express or overexpress the functional sodium channel.

17. The assay method of claim 15, wherein the host cell has been genetically engineered by the introduction into the cell of a nucleic acid molecule having a nucleotide sequence encoding a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2).

18. The assay method of claim 15, wherein the host cell has been genetically engineered to upregulate the expression of a nucleic acid encoding a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2),

19. The assay method of claim 18, wherein the upregulated nucleic acid is endogenous to the host cell.

20. The assay method of claim 15, wherein the modulation of the functional sodium channel activity is antagonism of that activity.

21. The assay method of claim 15, wherein the modulation of the functional sodium channel activity is agonism of that activity.

FIGURE 1: NaIII18 cDNA (SEQ ID NO: 1)

```
tgaaaagatggcacaggcactgttggtacccccaggacctgaaagcttccgccttttttactaga
gaatctcttgctgctatcgaaaaacgtgctgcagaagagaaagccaagaagcccaaaaaggaac
aagataatgatgatgagaacaaaccaaagccaaatagtgacttggaagctggaaagaaccttcc
atttatttatggagacattcctccagagatggtgtcagagcccctggaggacctggatccctac
tatatcaataagaaaacttttatagtaatgaataaaggaaaggcaattttccgattcagtgcca
cctctgccttgtatattttaactccactaaaccctgttaggaaaattgctatcaagattttggt
acattctttattcagcatgcttatcatgtgcactattttgaccaactgtgtatttatgaccttg
agcaaccctcctgactggacaaagaatgtagagtacacattcactggaatctatacctttgagt
cacttataaaaatcttggcaagagggttttgcttagaagattttacgtttcttcgtgatccatg
gaactggctggatttcagtgtcattgtgatggcgtatgtaacagaatttgtaagcctaggcaat
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gcagatgctcgaacagcttaaaaagcaacaggaagaagctcaggcagttgcggcagcatcagct
gcttcaagagatttcagtggaataggtgggttaggagagctgttggaaagttcttcagaagcat
caaagttgagttccaaaagtgctaaagaatggaggaaccgaaggaagaaaagaagacggagaga
gcaccttgaaggaaacaacaaggagagagagacagctttcccaaatccgaatctgaagacagc
gtcaaaagaagcagcttccttttctccatggatggaaacagactgaccagtgacaaaaaattct
gctcccctcatcagtctctcttgagtatccgtggctccctgttttccccaagacgcaatagcaa
aacaagcattttcagtttcagaggtcgggcaaaggatgttggatctgaaaatgactttgctgat
gatgaacacagcacatttgaagacagcgaaagcaggagagactcactgtttgtgccgcacagac
atggagagcgacgcaacagtaacgttagtcaggccagtatgtcatccaggatggtgccagggct
tccagcaaatgggaagatgcacagcactgtggattgcaatggtgtggtttccttggtgggtgga
ccttcagctctaacgtcacctactggacaacttcccccagagggcaccaccacagaaacggaag
tcagaaagagaaggttaagctcttaccagatttcaatggagatgctggaggattcctctggaag
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cagaaatgtccgccatgctggtatagatttgccaatgtgttcttgatctgggactgctgtgatg
catggttaaaagtaaacatcttgtgaatttaattgttatggatccatttgttgatcttgccat
cactatttgcattgtcttaaatacctctttatggccatggagcactaccccatgactgagcaa
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tattgtcagcctcagtttaatggagcttggtctgtcaaatgtggagggattgtctgtactgcga
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agatcattggcaattctgtgggggctctaggaaacctcaccttggtgttggccatcatcgtctt
catttttgctgtggtcggcatgcagctctttggtaagagctacaaagaatgtgtctgcaagatc
aatgatgactgtacgctcccacggtggcacatgaacgacttcttccactccttcctgattgtgt
```

FIGURE 1 (continued)

```
tccgcgtgctgtgtggagagtggatagagaccatgtgggactgtatggaggtcgctggccaaac
catgtgccttattgttttcatgttggtcatggtcattggaaaccttgtggttctgaacctcttt
ctggccttattgttgagttcatttagctcagacaaccttgctgctactgatgatgacaatgaaa
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gcgggagtgtttccaaaaagccttttttagaaagccaaaagttatagaaatccatgaaggcaat
aagatagacagctgcatgtccaataatactggaattgaaataagcaaagagcttaattatctta
gagatgggaatggaaccaccagtggtgtaggtactggaagcagtgttgaaaaatacgtaatcga
tgaaaatgattatatgtcattcataaacaaccccagcctcaccgtcacagtgccaattgctgtt
ggagagtctgactttgaaaacttaaatactgaagagttcagcagtgagtcagaactagaagaaa
gcaaagagaaattaaatgcaaccagctcatctgaaggaagcacagttgatgttgttctaccccg
agaaggtgaacaagctgaaactgaacccgaagaagaccttaaaccggaagcttgttttactgaa
ggatgtattaaaaagtttccattctgtcaagtaagtacagaagaaggcaaagggaagatctggt
ggaatcttcgaaaaacctgctacagtattgttgagcacaactggtttgagactttcattgtgtt
catgatccttctcagtagtggtgcattggcctttgaagatatatacattgaacagcgaaagact
atcaaaaccatgctagaatatgctgacaaagtctttacctatatattcattctggaaatgcttc
tcaaatgggttgcttatggatttcaaacatatttcactaatgcctggtgctggctagatttctt
gatcgttgatgtttctttggttagcctggtagccaatgctcttggctactcagaactcggtgcc
atcaaatcattacggacattaagagctttaagacctctaagagccttatcccggtttgaaggca
tgagggtggttgtgaatgctcttgttggagcaattccctctatcatgaatgtgctgttggtctg
tctcatcttctggttgatctttagcatcatgggtgtgaatttgtttgctggcaagttctaccac
tgtgttaacatgacaacgggtaacatgtttgacattagtgatgttaacaatttgagtgactgtc
aggctcttggcaagcaagctcggtggaaaaacgtgaaagtaaactttgataatgttggcgctgg
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gattcacgagatgttaaacttcagcctgtatatgaagaaatctgtacatgtatttatactttg
tcatctttatcatctttgggtcattcttcactctgaatctattcattggtgtcatcatagataa
cttcaaccagcagaaaaagaagtttggaggtcaagacatctttatgacagaggaacagaaaaaa
tattacaatgcaatgaagaaacttggatccaagaaacctcagaaacccatacctcgcccagcaa
acaaattccaaggaatggtctttgattttgtaaccagacaagtctttgatatcagcatcatgat
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tctctccattgtaggtatgtttctggctgagatgatagaaaagtattttgtgtcccctaccttg
ttccgagtgatccgtcttgccaggattggccgaatcctacgtctgatcaaaggagcaaagggga
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gctggaattgatgacatgttcaactttgagacctttggcaacagcatgatctgcttgttccaaa
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agcttattgccatggatctgcccatggtcagtggtgaccggatccactgtcttgatattttatt
tgcctttacaaagcgtgttttgggtgagagtggagagatggatgcccttcgaatacagatggaa
gacaggtttatggcatcaaacccctccaaagtctcttatgagcctattacaaccactttgaaac
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FIGURE 1 (continued)

```
gtaaacaagaggaggtgtctgccgctatcattcagcgtaatttcagatgttatcttttaaagca
aaggttaaaaaatatatcaagtaactataacaaagaggcaattaaagggaggattgacttacct
ataaaacaagacatgattattgacaaactaaatgggaactccactccagaaaaaacagatggga
gttcctctaccacctctcctccttcctatgatagtgtaacaaaaccagacaaggaaaagtttga
gaaagacaaaccagaaaaagaaagcaaaggaaaagaggtcagagaaaatcaaaagtaaaaagaa
acaaagaattatctttgtgatcaattgtttacagcctatga
```

FIGURE 2: NaIII18 amino acid (SEQ ID NO: 2)

MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKEQDNDDENKPKPNSDLEAG
KNLPFIYGDIPPEMVSEPLEDLDPYYINKKTFIVMNKGKAIFRFSATSALYILTPLNPVR
KIAIKILVHSLFSMLIMCTILTNCVFMTLSNPPDWTKNVEYTFTGIYTFESLIKILARGF
CLEDFTFLRDPWNWLDFSVIVMAYVTEFVSLGNVSALRTFRVLRALKTISVIPGLKTIVG
ALIQSVKKLSDVMILTVFCLSVFALIGLQLFMGNLRNKCLQWPPSDSAFETNTTSYFNGT
MDSNGTFVNVTMSTFNWKDYIGDDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRN
PNYGYTSFDTFSWAFLSLFRLMTQDYWENLYQLTLRAAGKTYMIFFVLVIFLGSFYLVNL
ILAVVAMAYEEQNQATLEEAEQKEAEFQQMLEQLKKQQEEAQAVAAASAASRDFSGIGGL
GELLESSSEASKLSSKSAKEWRNRRKKRRRREHLEGNNKGERDSFPKSESEDSVKRSSFL
FSMDGNRLTSDKKFCSPHQSLLSIRGSLFSPRRNSKTSIFSFRGRAKDVGSENDFADDEH
STFEDSESRRDSLFVPHRHGERRNSNVSQASMSSRMVPGLPANGKMHSTVDCNGVVSLVG
GPSALTSPTGQLPPEGTTTETEVRKRRLSSYQISMEMLEDSSGRQRAVSIASILTNTMEE
LEESRQKCPPCWYRFANVFLIWDCCDAWLKVKHLVNLIVMDPFVDLAITICIVLNTLFMA
MEHYPMTEQFSSVLTVGNLVFTGIFTAEMVLKIIAMDPYYYFQEGWNIFDGIIVSLSLME
LGLSNVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVGALGNLTLVLAIIVFIFAV
VGMQLFGKSYKECVCKINDDCTLPRWHMNDFFHSFLIVFRVLCGEWIETMWDCMEVAGQT
MCLIVFMLVMVIGNLVVLNLFLALLLSSFSSDNLAATDDDNEMNNLQIAVGRMQKGIDYV
KNKMRECFQKAFFRKPKVIEIHEGNKIDSCMSNNTGIEISKELNYLRDGNGTTSGVGTGS
SVEKYVIDENDYMSFINNPSLTVTVPIAVGESDFENLNTEEFSSESELEESKEKLNATSS
SEGSTVDVVLPREGEQAETEPEEDLKPEACFTEGCIKKFPFCQVSTEEGKGKIWWNLRKT
CYSIVEHNWFETFIVFMILLSSGALAFEDIYIEQRKTIKTMLEYADKVFTYIFILEMLLK
WVAYGFQTYFTNAWCWLDFLIVDVSLVSLVANALGYSELGAIKSLRTLRALRPLRALSRF
EGMRVVVNALVGAIPSIMNVLLVCLIFWLIFSIMGVNLFAGKFYHCVNMTTGNMFDISDV
NNLSDCQALGKQARWKNVKVNFDNVGAGYLALLQVATFKGWMDIMYAAVDSRDVKLQPVY
EENLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFNQQKKKFGGQDIFMTEEQKKYYNAMKK
LGSKKPQKPIPRPANKFQGMVFDFVTRQVFDISIMILICLNMVTMMVETDDQGKYMTLVL
SRINLVFIVLFTGEFVLRLVSLRHYYFTIGWNIFDFVVVILSIVGMFLAEMIEKYFVSPT
LFRVIRLARIGRILRLIKGAKGIRTLLFALMMSLPALFNIGLLLFLVMFIYAIFGMSNFA
YVKKEAGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILNSAPPDCDPDTIHPGSSVK
GDCGNPSVGIFFFVSYIIISFLVVVNMYIAVILENFSVATEESAEPLSEDDFEMFYEVWE
KFDPDATQFIEFSKLSDFAAALDPPLLIAKPNKVQLIAMDLPMVSGDRIHCLDILFAFTK
RVLGESGEMDALRIQMEDRFMASNPSKVSYEPITTTLKRKQEEVSAAIIQRNFRCYLLKQ
RLKNISSNYNKEAIKGRIDLPIKQDMIIDKLNGNSTPEKTDGSSSTTSPPSYDSVTKPDK
EKFEKDKPEKESKGKEVRENQK

FIGURE 3: cDNA sequence of human SCN3A of Clare et al. (SEQ ID NO: 3)

```
   1 taccctaacc atcttggatg ctgggctttg ttatgctgta attcataagg ctctgtttta
  61 tcagagatta tggagcaaga aaactgaagc caagccacat caaggtttga cagggatgag
 121 atacctgtca aggattcata gtagagtggc ttactgggaa aggagcaaag aatctcttct
 181 agggatattg taagaataaa tgagataatt cacagaaggg acctggagct tttccggaaa
 241 aaggtgctgt gactatctaa ggtaattcgt atgcaagaag ctacacgtaa ttaaatgtgc
 301 aggatgaaaa gatggcacag gcactgttgg tacccccagg acctgaaagc ttccgccttt
 361 ttactagaga atctcttgct gctatcgaaa aacgtgctgc agaagagaaa gccaagaagc
 421 ccaaaaagga acaagataat gatgatgaga acaaaccaaa gccaaatagt gacttggaag
 481 ctggaaagaa ccttccattt atttatggag acattcctcc agagatggtg tcagagcccc
 541 tggaggacct ggatccctac tatatcaata agaaaacttt tatagtaatg aataaaggaa
 601 aggcaatttt ccgattcagt gccacctctg ccttgtatat tttaactcca ctaaaccctg
 661 ttaggaaaat tgctatcaag attttggtac attctttatt cagcatgctt atcatgtgca
 721 ctattttgac caactgtgta tttatgacct tgagcaaccc tcctgactgg acaaagaatg
 781 tagagtacac attcactgga atctatacct ttgagtcact tataaaaatc ttggcaagag
 841 ggttttgctt agaagatttt acgttcttc gtgatccatg gaactggctg gatttcagtg
 901 tcattgtgat ggcgtatgta acagaatttg taagcctagg caatgtttca gcccttcgaa
 961 ctttcagagt cttgagagct ctgaaaacta tttctgtaat tccaggttta aagaccattg
1021 tggggcccct gatccagtcg gtaaagaagc tttctgatgt gatgatcctg actgtgttct
1081 gtctgagcgt gtttgctctc attgggctgc agctgttcat gggcaatctg aggaataaat
1141 gtttgcagtg gccccaagc gattctgctt ttgaaaccaa caccacttcc tactttaatg
1201 gcacaatgga ttcaaatggg acatttgtta atgtaacaat gagcacattt aactggaagg
1261 attacattgg agatgacagt cactttatg ttttggatgg gcaaaaagac cctttactct
1321 gtggaaatgg ctcagatgca ggccagtgtc cagaaggata catctgtgtg aaggctggtc
1381 gaaaccccaa ctatggctac acaagctttg acacctttag ctgggctttc tgtctctat
1441 ttcgactcat gactcaagac tactgggaaa atctttacca gttgacatta cgtgctgctg
1501 ggaaaacata catgatattt tttgtcctgg tcattttctt gggctcattt tatttggtga
1561 atttgatcct ggctgtggtg gccatggcct atgaggagca gaatcaggcc accttggaag
1621 aagcagaaca aaaagaggcc gaattcagc agatgctcga acagcttaaa aagcaacagg
1681 aagaagctca ggcagttgcg gcagcatcag ctgcttcaag agatttcagt ggaataggtg
1741 ggttaggaga gctgttggaa agttcttcag aagcatcaaa gttgagttcc aaaagtgcta
1801 aagaatggag gaaccgaagg aagaaaagaa gacagagaga gcaccttgaa ggaaacaaca
1861 aaggagagag agacagcttt cccaaatccg aatctgaaga cagcgtcaaa agaagcagct
1921 tccttttctc catggatgga aacagactga ccagtgacaa aaaattctgc tcccctcatc
1981 agtctctctt gagtatccgt ggctccctgt tttccccaag acgcaatagc aaaacaagca
2041 ttttcagttt cagaggtcgg gcaaaggatg ttggatctga aaatgacttt gctgatgatg
2101 aacacagcac atttgaagac agcgaaagca ggagagactc actgtttgtg ccgcacagac
2161 atggagagcg acgcaacagt aacggcacca ccactgaaac ggaagtcaga aagagaaggt
2221 taagctctta ccagatttca atggagatgc tggaggattc ctctggaagg caaagagccg
2281 tgagcatagc cagcattctg accaacacaa tggaagaact tgaagaatct agacagaaat
2341 gtccgccatg ctggtataga tttgccaatg tgttcttgat ctgggactgc tgtgatgcat
2401 ggttaaaagt aaaacatctt gtgaatttaa ttgttatgga tccatttgtt gatcttgcca
2461 tcactatttg cattgtctta aatacctct ttatggccat ggagcactac cccatgactg
2521 agcaattcag tagtgtgttg actgtaggaa acctggtctt tactgggatt ttcacagcag
2581 aaatggttct caagatcatt gccatggatc cttattacta tttccaagaa ggctggaata
2641 tctttgatgg aattattgtc agcctcagtt taatggagct tggtctgtca aatgtggagg
2701 gattgtctgt actgcgatca ttcagactgc ttagagtttt caagttggca aaatcctggc
2761 ccacactaaa tatgctaatt aagatcattg caattctgt ggggctcta ggaaacctca
2821 ccttggtgtt ggccatcatc gtcttcattt ttgctgtggt cggcatgcag ctctttggta
2881 agagctacaa agaatgtgtc tgcaagatca atgatgactg tacgctccca cggtggcaca
2941 tgaacgactt cttccactcc ttcctgattg tgttccgcgt gctgtgtgga gagtggatag
3001 agaccatgtg ggactgtatg gaggtcgctg gccaaaccat gtgccttatt gttttcatgt
3061 tggtcatggt cattggaaac cttgtggttc tgaacctctt ctggcctta ttgttgagtt
3121 catttagctc agacaacctt gctgctactg atgatgacaa tgaaatgaat aatctgcaga
```

FIGURE 3 (continued)

```
3181  ttgcagtagg  aagaatgcaa  aagggaattg  attatgtgaa  aaataagatg  cgggagtgtt
3241  tccaaaaagc  cttttttaga  aagccaaaag  ttatagaaat  ccatgaaggc  aataagatag
3301  acagctgcat  gtccaataat  actggaattg  aaataagcaa  agagcttaat  tatcttagag
3361  atgggaatgg  aaccaccagt  ggtgtaggta  ctggaagcag  tgttgaaaaa  tacgtaatcg
3421  atgaaaatga  ttatatgtca  ttcataaaca  accccagcct  caccgtcaca  gtgccaattg
3481  ctgttggaga  gtctgacttt  gaaaacttaa  atactgaaga  gttcagcagt  gagtcagaac
3541  tagaagaaag  caaagagaaa  ttaaatgcaa  ccagctcatc  tgaaggaagc  acagttgatg
3601  ttgttctacc  ccgagaaggt  gaacaagctg  aaactgaacc  cgaagaagac  cttaaaccgg
3661  aagcttgttt  tactgaagga  tgtattaaaa  agtttccatt  ctgtcaagta  agtacagaag
3721  aaggcaaagg  gaagatctgg  tggaatcttc  gaaaaacctg  ctacagtatt  gttgagcaca
3781  actggtttga  gactttcatt  gtgttcatga  tccttctcag  tagtggtgca  ttggcctttg
3841  aagatatata  cattgaacag  cgaaagacta  tcaaaaccat  gctagaatat  gctgacaaag
3901  tctttaccta  tatattcatt  ctggaaatgc  ttctcaaatg  ggttgcttat  ggatttcaaa
3961  catatttcac  taatgcctgg  tgctggctag  atttcttgat  cgttgatgtt  tctttggtta
4021  gcctggtagc  caatgctctt  ggctactcag  aactcggtgc  catcaaatca  ttacggacat
4081  taagagcttt  aagacctcta  agagccttat  cccggtttga  aggcatgagg  gtggttgtga
4141  atgctcttgt  tggagcaatt  ccctctatca  tgaatgtgct  gttggtctgt  ctcatcttct
4201  ggttgatctt  tagcatcatg  ggtgtgaatt  tgtttgctgg  caagttctac  cactgtgtta
4261  acatgacaac  gggtaacatg  tttgacatta  gtgatgttaa  caatttgagt  gactgtcagg
4321  ctcttggcaa  gcaagctcgg  tggaaaaacg  tgaaagtaaa  ctttgataat  gttggcgctg
4381  gctatcttgc  actgcttcaa  gtggccacat  ttaaaggctg  gatggatatt  atgtatgcag
4441  ctgttgattc  acgagatgtt  aaacttcagc  ctgtatatga  agaaatctg  tacatgtatt
4501  tatactttgt  catctttatc  atctttgggt  cattcttcac  tctgaatcta  ttcattggtg
4561  tcatcataga  taacttcaac  cagcagaaaa  agaagtttgg  aggtcaagac  atctttatga
4621  cagaggaaca  gaaaaaatat  tacaatgcaa  tgaagaaact  tggatccaag  aaacctcaga
4681  aacccatacc  tcgcccagca  aacaaattcc  aaggaatggt  ctttgatttt  gtaaccagac
4741  aagtctttga  tatcagcatc  atgatcctca  tctgcctcaa  catggtcacc  atgatggtgg
4801  aaacggatga  ccagggcaaa  tacatgaccc  tagttttgtc  ccggatcaac  ctagtgttca
4861  ttgttctgtt  cactggagaa  tttgtgctga  agctcgtctc  cctcagacac  tactacttca
4921  ctataggctg  gaacatcttt  gactttgtgg  tggtgattct  ctccattgta  ggtatgtttc
4981  tggctgagat  gatagaaaag  tattttgtgt  cccctacctt  gttccgagtg  atccgtcttg
5041  ccaggattgg  ccgaatccta  cgtctgatca  aggagcaaa  ggggatccgc  acgctgctct
5101  ttgctttgat  gatgtccctt  cctgcgttgt  ttaacatcgg  cctcctgctc  ttcctggtca
5161  tgtttatcta  tgccatcttt  gggatgtcca  actttgccta  tgttaaaaag  gaagctggaa
5221  ttgatgacat  gttcaacttt  gagacctttg  gcaacagcat  gatctgcttg  ttccaaatta
5281  caacctctgc  tggctgggat  ggattgctag  cacctattct  taatagtgca  ccacccgact
5341  gtgaccctga  cacaattcac  cctggcagct  cagttaaggg  agactgtggg  aacccatctg
5401  ttgggatttt  cttttttcgtc  agttacatca  tcatatcctt  cctggttgtg  gtgaacatgt
5461  acatcgcggt  catcctggag  aacttcagtg  ttgctactga  agaaagtgca  gagcccctga
5521  gtgaggatga  ctttgagatg  ttctatgagg  tttgggaaaa  gtttgatccc  gatgcgaccc
5581  agtttataga  gttctctaaa  ctctctgatt  ttgcagctgc  cctggatcct  cctcttctca
5641  tagcaaaacc  caacaaagtc  cagcttattg  ccatggatct  gcccatggtc  agtggtgacc
5701  ggatccactg  tcttgatatt  ttatttgcct  ttacaaagcg  tgtttttgggt  gagagtggag
5761  agatggatgc  ccttcgaata  cagatggaag  acaggtttat  ggcatcaaac  ccctccaaag
5821  tctcttatga  gcctattaca  accactttga  aacgtaaaca  agaggaggtg  tctgccgcta
5881  tcattcagcg  taatttcaga  tgttatcttt  taaagcaaag  gttaaaaaat  atatcaagta
5941  actataacaa  agaggcaatt  aaagggagga  ttgacttacc  tataaaacaa  gacatgatta
6001  ttgacaaact  aaatgggaac  tccactccag  aaaaaacaga  tgggagttcc  tctaccacct
6061  ctcctccttc  ctatgatagt  gtaacaaaac  cagacaagga  aaagtttgag  aaagacaaac
6121  cagaaaaaga  aagcaaagga  aaagaggtca  gagaaaatca  aaagtaaaaa  gaaacaaaga
6181  attatctttg  tgatcaattg  tttacagcct  atgaaggtaa  agtatatgtg  tcaactggac
6241  ttcaagagga  ggtccatgcc  aaactgactg  ttttaacaaa  tactcatagt  cagtgcctat
6301  acaagacagt  gaagtgacct  ctctgtcact  gcaactctgt  gaagcagggt  atcaacattg
6361  acaagaggtt  gctgttttta  ttaccagctg  acactgctga  ggagaaaccc  aatggctacc
```

FIGURE 3 (continued)

```
6421 tagactatag ggatagttgt gcaaagtgaa cattgtaact acaccaaaca cctttagtac
6481 agtccttgca tccattctat ttttaacttc catatctgcc atatttttac aaaatttgtt
6541 ctagtgcatt tccatggtcc ccaattcata gtttattcat aatgctatgt cactatttt
```

FIGURE 4: amino acid sequence of human SCN3A (SEQ ID NO: 4)

MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKEQDNDDENKPKPNSDLEAGKNLPFI
YGDIPPEMVSEPLEDLDPYYINKKTFIVMNKGKAIFRFSATSALYILTPLNPVRKIAIKILVHS
LFSMLIMCTILTNCVFMTLSNPPDWTKNVEYTFTGIYTFESLIKILARGFCLEDFTFLRDPWNW
LDFSVIVMAYVTEFVSLGNVSALRTFRVLRALKTISVIPGLKTIVGALIQSVKKLSDVMILTVF
CLSVFALIGLQLFMGNLRNKCLQWPPSDSAFETNTTSYFNGTMDSNGTFVNVTMSTFNWKDYIG
DDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRNPNYGYTSFDTFSWAFLSLFRLMTQDY
WENLYQLTLRAAGKTYMIFFVLVIFLGSFYLVNLILAVVAMAYEEQNQATLEEAEQKEAEFQQM
LEQLKKQQEEAQAVAAASAASRDFSGIGGLGELLESSSEASKLSSKSAKEWRNRRKKRRQREHL
EGNNKGERDSFPKSESEDSVKRSSFLFSMDGNRLTSDKKFCSPHQSLLSIRGSLFSPRRNSKTS
IFSFRGRAKDVGSENDFADDEHSTFEDSESRRDSLFVPHRHGERRNSNGTTTETEVRKRRLSSY
QISMEMLEDSSGRQRAVSIASILTNTMEELEESRQKCPPCWYRFANVFLIWDCCDAWLKVKHLV
NLIVMDPFVDLAITICIVLNTLFMAMEHYPMTEQFSSVLTVGNLVFTGIFTAEMVLKIIAMDPY
YYFQEGWNIFDGIIVSLSLMELGLSNVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVGA
LGNLTLVLAIIVFIFAVVGMQLFGKSYKECVCKINDDCTLPRWHMNDFFHSFLIVFRVLCGEWI
ETMWDCMEVAGQTMCLIVFMLVMVIGNLVVLNLFLALLLSSFSSDNLAATDDDNEMNNLQIAVG
RMQKGIDYVKNKMRECFQKAFFRKPKVIEIHEGNKIDSCMSNNTGIEISKELNYLRDGNGTTSG
VGTGSSVEKYVIDENDYMSFINNPSLTVTVPIAVGESDFENLNTEEFSSESELEESKEKLNATS
SSEGSTVDVVLPREGEQAETEPEEDLKPEACFTEGCIKKFPFCQVSTEEGKGKIWWNLRKTCYS
IVEHNWFETFIVFMILLSSGALAFEDIYIEQRKTIKTMLEYADKVFTYIFILEMLLKWVAYGFQ
TYFTNAWCWLDFLIVDVSLVSLVANALGYSELGAIKSLRTLRALRPLRALSRFEGMRVVVNALV
GAIPSIMNVLLVCLIFWLIFSIMGVNLFAGKFYHCVNMTTGNMFDISDVNNLSDCQALGKQARW
KNVKVNFDNVGAGYLALLQVATFKGWMDIMYAAVDSRDVKLQPVYEENLYMYLYFVIFIIFGSF
FTLNLFIGVIIDNFNQQKKKFGGQDIFMTEEQKKYYNAMKKLGSKKPQKPIPRPANKFQGMVFD
FVTRQVFDISIMILICLNMVTMMVETDDQGKYMTLVLSRINLVFIVLFTGEFVLKLVSLRHYYF
TIGWNIFDFVVVILSIVGMFLAEMIEKYFVSPTLFRVIRLARIGRILRLIKGAKGIRTLLFALM
MSLPALFNIGLLLFLVMFIYAIFGMSNFAYVKKEAGIDDMFNFETFGNSMICLFQITTSAGWDG
LLAPILNSAPPDCDPDTIHPGSSVKGDCGNPSVGIFFFVSYIIISFLVVVNMYIAVILENFSVA
TEESAEPLSEDDFEMFYEVWEKFDPDATQFIEFSKLSDFAAALDPPLLIAKPNKVQLIAMDLPM
VSGDRIHCLDILFAFTKRVLGESGEMDALRIQMEDRFMASNPSKVSYEPITTTLKRKQEEVSAA
IIQRNFRCYLLKQRLKNISSNYNKEAIKGRIDLPIKQDMIIDKLNGNSTPEKTDGSSSTTSPPS
YDSVTKPDKEKFEKDKPEKESKGKEVRENQK

FIGURE 5: cDNA of human sodium channel a-subunit variant by Jeong et al. (SEQ ID NO: 5)

```
   1 agcgaagcgg aggcataagc agagaggatt ctggaaaggt ctctttgttt tcttatccac
  61 agagaaagaa agaaaaaaaa ttgtaactaa tttgtaaacc tctgtggtca aaaaaaaaaa
 121 aaaaaaaaaa gctgaacagc tgccagagga agacacgtta taccctaacc atcttggatg
 181 ctgggctttg ttatgctgta attcataagg ctctgtttta tcagagatta tggagcaaga
 241 aaactgaagc caagccacat caaggtttga cagggatgag atacctgtca aggattcata
 301 gtagagtggc ttactgggaa aggagcaaag aatctcttct agggatattg taagaataaa
 361 tgagataatt cacagaaggg acctggagct tttccggaaa aaggtgctgt gactatctaa
 421 ggtaattcgt atgcaagaag ctacacgtaa ttaaatgtgc aggatgaaaa gatggcacag
 481 gcactgttgg tacccccagg acctgaaagc ttccgccttt ttactagaga atctcttgct
 541 gctatcgaaa aacgtgctgc agaagagaaa gccaagaagc ccaaaaagga acaagataat
 601 gatgatgaga acaaaccaaa gccaaatagt gacttggaag ctggaaagaa ccttccattt
 661 atttatggag acattcctcc agagatggtg tcagagcccc tggaggacct ggatccctac
 721 tatatcaata agaaaacttt tatagtaatg aataaggaa aggcaatttt ccgattcagt
 781 gccacctctg ccttgtatat tttaactcca ctaaaccctg ttaggaaaat tgctatcaag
 841 attttggtac attctttatt cagcatgctt atcatgtgca ctattttgac caactgtgta
 901 tttatgacct tgagcaaccc tcctgactgg acaaagaatg tagagtacac attcactgga
 961 atctatacct ttgagtcact tataaaaatc ttggcaagag ggttttgctt agaagatttt
1021 acgtttcttc gtgatccatg gaactggctg gatttcagtg tcattgtgat ggcatatgtg
1081 acagagtttg tggacctggg caatgtctca gcgttgagaa cattcagagt tctccgagca
1141 ctgaaaacaa tttcagtcat tccaggttta aagaccattg tggggcccct gatccagtcg
1201 gtaaagaagc tttctgatgt gatgatcctg actgtgttct gtctgagcgt gtttgctctc
1261 attgggctgc agctgttcat gggcaatctg aggaataaat gtttgcagtg gccccccaagc
1321 gattctgctt ttgaaaccaa caccacttcc tactttaatg gcacaatgga ttcaaatggg
1381 acatttgtta atgtaacaat gagcacattt aactggaagg attacattgg agatgacagt
1441 cacttttatg ttttggatgg gcaaaaagac cctttactct gtggaaatgg ctcagatgca
1501 ggccagtgtc cagaaggata catctgtgtg aaggctggtc gaaaccccaa ctatggctac
1561 acaagctttg acacctttag ctgggctttc ctgtctctat ttcgactcat gactcaagac
1621 tattgggaaa atctttacca gttgacatta cgtgctgctg gaaaacata catgatattt
1681 tttgtcctgg tcattttctt gggctcattt tatttggtga atttgatcct ggctgtggtg
1741 gccatggcct atgaggagca gaatcaggcc accttggaag aagcagaaca aaaagaggcc
1801 gaatttcagc agatgctcga acagcttaaa aagcaacagg aagaagctca ggcagttgcg
1861 gcagcatcag ctgcttcaag agatttcagt ggagtaggtg ggttaggaga gctgttggaa
1921 agttcttcag aagcatcaaa gttgagttcc aaaggtgcta agaatggag gaaccggagg
1981 aagaaaagaa gacagagaga gcaccttgaa ggaaacaaca aggagagag agacagcttt
2041 cccaaatccg aatctgaaga cagcgtcaaa agaagcagct tccttttctc catggatgga
2101 aacagactga ccagtgacaa aaaattctgc tcccctcatc agtctctctt gagtatccgt
2161 ggctccctgt tttccccaag acgcaatagc aaaacaagca ttttcagttt cagaggtcgg
2221 gcaaaggatg ttggatctga aaatgacttt gctgatgatg aacacagcac atttgaagac
2281 ggcgaaagca ggagagactc actgtttgtg ccgcacagac atggagagcg acgcaacagt
2341 aacgttagtc aggccagtat gtcatccagg atggtgccag ggcttccagc aaatgggaag
2401 atgcacagca ctgtggattg caatggtgtg gtttccttgg tgggtggacc ttcagctcta
2461 acgtcaccta ctggacaact tccccagag ggcaccacca ctgaaacgga agtcagaaag
2521 agaaggttaa gctcttacca gatttcaatg gagatgctgg aggattcctc tggaaggcaa
2581 agagccgtga gcatagccag cattctgacc aacacaatgg aagaacttga gaatctaga
2641 cagaaatgtc cgccatgctg gtatagattt gccaatgtgt tcttgatctg ggactgctgt
2701 gatgcatggt aaaagtaaa acatcttgtg aatttaattg ttatggatcc atttgttgat
2761 cttgccatca ctatttgcat tgtcttaaat accctcttta tggccatgga gcactacccc
2821 atgactgagc aattcagtag tgtgttgact gtaggaaacc tggtctttac tgggatttttc
2881 acagcagaaa tggttctcaa gatcattgcc atggatcctt attactattt ccaagaaggc
2941 tggaatatct ttgatggaat tattgtcagc ctcagtttaa tggagcttgg tctgtcaaat
3001 gtggagggat tgtctgtact gcgatcattc agactgctta gagttttcaa gttggcaaaa
3061 tcctggccca cactaaatat gctaattaag atcattggca attctgtggg ggctctagga
3121 aacctcacct tggtgttggc catcatcgtc ttcattttttg ctgtggtcgg catgcagctc
```

FIGURE 5 (continued)

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3181 tttggtaaga gctacaaaga atgtgtctgc aagatcaatg atgactgtac gctcccacgg
3241 tggcacatga acgacttctt ccactccttc ctgattgtgt tccgcgtgct gtgtggagag
3301 tggatagaga ccatgtggga ctgtatggag gtcgctggcc aaaccatgtg ccttattgtt
3361 ttcatgttgg tcatggtcat tggaaacctt gtggttctga acctctttct ggccttatta
3421 ttgagttcat ttagctcaga caaccttgct gctactgatg atgacaatga aatgaataat
3481 ctgcagattg cagtaggaag aatgcaaaag ggaattgatt atgtgaaaaa taagatgcgg
3541 gagtgtttcc aaaaagcctt ttttagaaag ccaaaagtta tagaaatcca tgaaggcaat
3601 aagatagaca gctgcatgtc caataatact ggaattgaaa taagcaaaga gcttaattat
3661 cttagagatg ggaatggaac caccagtggt gtaggtactg aagcagtgt tgaaaaatac
3721 gtaatcgatg aaaatgatta tatgtcattc ataaacaacc ccagcctcac cgtcacagtg
3781 ccaattgctg ttggagagtc tgactttgaa aacttaaata ctgaagagtt cagcagtgag
3841 tcagaactag aagaaagcaa agagaaatta aatgcaacca gctcatctga aggaagcaca
3901 gttgatgttg ttctaccccg agaaggtgaa caagctgaaa ctgaacccga agaagacttt
3961 aaaccggaag cttgttttac tgaagggtgt attaaaaagt ttccattctg tcaagtaagt
4021 acagaagaag gcaaagggaa gatctggtgg aatcttcgaa aaacctgcta cagtattgtt
4081 gagcacaact ggtttgagac tttcattgtg ttcatgatcc ttctcagtag tggtgcattg
4141 gcctttgaag atatatacat tgaacagcga aagactatca aaaccatgct agaatatgct
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4261 tttcaaacat atttcactaa tgcctggtgc tggctagatt tcttgatcgt tgatgtttct
4321 ttggttagcc tggtagccaa tgctcttggc tactcagaac tcggtgccat caaatcatta
4381 cggacattaa gagctttaag acctctaaga gccttatccc ggtttgaagg catgaggtg
4441 gttgtgaatg ctcttgttgg agcaattccc tctatcatga atgtgctgtt ggtctgtctc
4501 atcttctggt tgatctttag catcatgggt gtgaatttgt ttgctggcaa gttctaccac
4561 tgtgttaaca tgacaacggg taacatgttt gacattagtg atgttaacaa tttgagtgac
4621 tgtcaggctc ttggcaagca agctcggtgg aaaaacgtga agtaaacttt gataatgtt
4681 ggcgctggct atcttgcact gcttcaagtg gccacattta aaggctggat ggatattatg
4741 tatgcagctg ttgattcacg agatgttaaa cttcagcctg tatatgaaga aaatctgtac
4801 atgtatttat actttgtcat ctttatcatc tttgggtcat tcttcactct gaatctattc
4861 attggtgtca tcatagataa cttcaaccag cagaaaaaga gtttggagg tcaagacatc
4921 tttatgacag aggaacagaa aaaatattac aatgcaatga agaaacttgg atccaagaaa
4981 cctcagaaac ccatacctcg cccagcaaac aaattccaag gaatggtctt tgatttttgta
5041 accagacaag tctttgatat cagcatcatg atcctcatct gcctcaacat ggtcaccatg
5101 atggtggaaa cggatgacca gggcaaatac atgaccctag ttttgtcccg gatcaaccta
5161 gtgttcattg ttctgttcac tggagaattt gtgctgaagc tcgtttccct cagacactac
5221 tacttcacta taggctggaa catctttgac tttgtggtgg tgattctctc cattgtaggt
5281 atgtttctgg ctgagatgat agaaaagtat tctgtgtccc ctaccttgtt ccgagtgatc
5341 cgtcttgcca ggattggccg aatcctacgt ctgatcaaag gagcaaaggg gatccgcacg
5401 ctgctctttg ctttgatgat gtcccttcct gcgttgttta acatcggcct cctgctcttc
5461 ctggtcatgt ttatctatgc catctttggg atgtccaact ttgcctatgt taaaaaggaa
5521 gctggaattg atgacatgtt caactttgag accttggca acagcatgat ctgcttgttc
5581 caaattacaa cctctgctgg ctgggatgga ttgctagcac ctattcttaa tagtgcacca
5641 cccgactgtg accctgacac aattcaccct ggcagctcag ttaagggaga ccgtggggac
5701 ccatctgttg ggattttctt ttttgtcagt tacatcatca tatccttcct ggttgtggtg
5761 aacatgtaca tcgcggtcat cctggagaac ttcagtgttg ctactgaaga aagtgcagag
5821 cccctgagtg aggatgactt tgagatgttc tatgaggttt gggaaaagtt tgatcccgat
5881 gcgacccagt ttatagagtt ctctaaactc tctgattttg cagctgccct ggatcctcct
5941 cttctcatag caaaacccaa caaagtccag cttattgcca tggatctgcc catggtcagt
6001 ggtgaccgga tccactgtct tgatattttta tttgccttta caaagcgtgt tttgtgtgag
6061 agtggagaga tggatgccct tcgaatacag atggaagaca ggtttatggc atcaaacccc
6121 tccaaagtct cttatgagcc tattacaacc actttgaaac gtaaacaaga ggaggtgtct
6181 gccgctatca ttcagcgtaa tttcagatgt atctttttaa agcaaaggtt aaaaaatata
6241 tcaagtaact ataacaaaga ggcaattaaa gggaggattg acttacctat aaaacaagac
6301 atgattattg acaaactaaa tgggaactcc actccagaaa aacagatgg gagttcctct
6361 accacccctc ctccttccta tgatagtgta acaaaaccag acaaggaaaa gtttgagaaa
```

FIGURE 5 (continued)

```
6421 gacaaaccag aaaaagaaag caaaggaaaa gaggtcagag aaaatcaaaa gtaaaaagaa
6481 acaaagaatt atctttgtga tcaattgttt acagcctatg aaggtaaagt atatgtgtca
6541 actggacttc aagaggaggt ccatgccaaa ctgactgttt taacaaatac tcatagtcag
6601 tgcctataca agacagtgaa gtgacctctc tgtcactgca actctgtgaa gcagggtatc
6661 aacgttgaca agaggttgct gtttttatta ccagctgaca ctgctgagga gaaacccaat
6721 ggctacctag actataggga tagttgtgca aagtgaacat tgtaactaca ccaaacacct
6781 ttagtacagt ccttgcatcc attctatttt taacttccat atctgccata tttttacaaa
6841 atttgttcta gtgcatttcc atggtcccca attcatagtt tattcataat gctatgtcac
6901 tatttttgta aatgaggttt acgttgaaga aacagtatac aagaaccctg tctctcaaat
6961 gatcagacaa aggtgttttg ccagagagat aaaatttttg ctcaaaacca gaaaaagaat
7021 tgtaatggct acagtttcag ttacttccat tttctagatg gctttaattt tgaaagtatt
7081 ttagtctgtt atgtttgttt ctatctgaac agttatgtgc ctgtaaagtc tcctctaata
7141 tttaaaggat tatttttatg caaagtattc tgtttcagca agtgcaaatt ttattctaag
7201 tttcagagct ctatatttaa tttaggtcaa atgctttcca aaaagtaatc taataaatcc
7261 attctagaaa aatatatcta aagtattgct ttagaatagt tgttccactt tctgctgcag
7321 tattgctttg ccatcttctg ctctcagcaa agctgatagt ctatgtcaat taaataccct
7381 atgttatgta aatagttatt ttatcctgtg gtgcatgttt gggcaaatat atatatagcc
7441 tgataaacaa cttctattaa atcaaatatg taccacagtg tatgtgtctt ttgcaagctt
7501 ccaacaggga tgtatcctgt atcattcatt aaacatagtt taaaggctat cactaatgca
7561 tgttaatatt gcctatgctg ctctatttta ctcaatccat tcttcacaag tcttggttaa
7621 agaatgtcac atattggtga tagaatgaat tcaacctgct ctgtccatta tgtcaagcag
7681 aataatttga agctatttac aaacaccttt acttttgcac ttttaattca acatgagtat
7741 catatggtat ctctctggat ttcaaggaaa cacactggat actgcctact gacaaaacct
7801 attcttcata tttttgctaaa aatatgtcta aaacttgttt aaatataaat aatgtaaaaa
7861 tataatcaac tttatttgtc agcattttgt acataagaaa attatttca ggttgatgac
7921 atcacaattt attttacttt atgcttttgc ttttgatttt taatcacaat tccaaacttt
7981 tgaatccata agattttca atggataatt tcctaaaata aaagttagat aatgggtttt
8041 atggatttct ttgttataat atattttcta ccattccaat aggagataca ttggtcaaac
8101 actcaaacct agatcatttt ctaccaacta tggttgcctc aatataacct tttattcata
8161 gatgttttt tttattcaac ttttgtagta tttacgtatg cagactagtc ttattttttt
8221 aattcctgct gcactaaagc tattacaaat ataacatgga ctttgttctt tttagccatg
8281 aacaaagtgg caagttgtg caattaccta acatgatata aattttgtt ttttgcacaa
8341 accaaaagtt taatgttaat tcttttaca aaactattta ctgtagtgta ttgaagaact
8401 gcatgcaggg aattgctatt gctaaaaga atggtgagct acgtcattat tgagccaaaa
8461 gaataaattt cattttttat tgcatttcac ttattgggct ctggggtttt ttgttttgt
8521 tttttgctgt tggcagttta aaatatatat aattaataaa acctgtgctt gatctgacat
8581 ttgtatacat aaaagtttac atgaatttta caacaaacta gtgcatgatt caccaagcag
8641 tactacagaa caaaggcaaa ttaaaagcag ctttgtgaac ttttatgtgt gcaaaggatc
8701 aagttcacat gttccaactt tcaggtttga taataatagt agtaaccacc tacaatagct
8761 ttcaatttca attaactccc ttggctataa gcatctaaac tcatcttctt tcaatataat
8821 tgatgctatc tcctaattac ttggtggcta ataaatgtta cattctttgt tacttaaatg
8881 cattatataa actcctatgt atacataagg tattaatgat atagttattg agaatttata
8941 ttaacttttt tttcaagaac ccttggattt atgtgaggtc aaaaccaaac tcttattctc
9001 agtggaaaac tccagttgta atgcatattt ttaaagacaa tttggatcta aatatgtatt
9061 tcataattct cccataataa attatataag gtggaaaaaa aaaaaaaaaa aaaaaaaaaa
9121 aaa
```

FIGURE 6: amino acid sequence of human sodium channel α-subunit variant by Jeong et al. (SEQ ID NO: 6)

```
MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKEQDNDDENKPKPNSDLEAGKNLPFI
YGDIPPEMVSEPLEDLDPYYINKKTFIVMNKGKAIFRFSATSALYILTPLNPVRKIAIKILVHS
LFSMLIMCTILTNCVFMTLSNPPDWTKNVEYTFTGIYTFESLIKILARGFCLEDFTFLRDPWNW
LDFSVIVMAYVTEFVDLGNVSALRTFRVLRALKTISVIPGLKTIVGALIQSVKKLSDVMILTVF
CLSVFALIGLQLFMGNLRNKCLQWPPSDSAFETNTTSYFNGTMDSNGTFVNVTMSTFNWKDYIG
DDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRNPNYGYTSFDTFSWAFLSLFRLMTQDY
WENLYQLTLRAAGKTYMIFFVLVIFLGSFYLVNLILAVVAMAYEEQNQATLEEAEQKEAEFQQM
LEQLKKQQEEAQAVAAASAASRDFSGVGGLGELLESSSEASKLSSKGAKEWRNRRKKRRQREHL
EGNNKGERDSFPKSESEDSVKRSSFLFSMDGNRLTSDKKFCSPHQSLLSIRGSLFSPRRNSKTS
IFSFRGRAKDVGSENDFADDEHSTFEDGESRRDSLFVPHRHGERRNSNVSQASMSSRMVPGLPA
NGKMHSTVDCNGVVSLVGGPSALTSPTGQLPPEGTTTETEVRKRRLSSYQISMEMLEDSSGRQR
AVSIASILTNTMEELEESRQKCPPCWYRFANVFLIWDCCDAWLKVKHLVNLIVMDPFVDLAITI
CIVLNTLFMAMEHYPMTEQFSSVLTVGNLVFTGIFTAEMVLKIIAMDPYYYFQEGWNIFDGIIV
SLSLMELGLSNVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVGALGNLTLVLAIIVFIF
AVVGMQLFGKSYKECVCKINDDCTLPRWHMNDFFHSFLIVFRVLCGEWIETMWDCMEVAGQTMC
LIVFMLVMVIGNLVVLNLFLALLLSSFSSDNLAATDDDNEMNNLQIAVGRMQKGIDYVKNKMRE
CFQKAFFRKPKVIEIHEGNKIDSCMSNNTGIEISKELNYLRDGNGTTSGVGTGSSVEKYVIDEN
DYMSFINNPSLTVTVPIAVGESDFENLNTEEFSSESELEESKEKLNATSSSEGSTVDVVLPREG
EQAETEPEEDFKPEACFTEGCIKKFPFCQVSTEEGKGKIWWNLRKTCYSIVEHNWFETFIVFMI
LLSSGALAFEDIYIEQRKTIKTMLEYADKVFTYIFILEMLLKWVAYGFQTYFTNAWCWLDFLIV
DVSLVSLVANALGYSELGAIKSLRTLRALRPLRALSRFEGMRVVVNALVGAIPSIMNVLLVCLI
FWLIFSIMGVNLFAGKFYHCVNMTTGNMFDISDVNNLSDCQALGKQARWKNVKVNFDNVGAGYL
ALLQVATFKGWMDIMYAAVDSRDVKLQPVYEENLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFN
QQKKKFGGQDIFMTEEQKKYYNAMKKLGSKKPQKPIPRPANKFQGMVFDFVTRQVFDISIMILI
CLNMVTMMVETDDQGKYMTLVLSRINLVFIVLFTGEFVLKLVSLRHYYFTIGWNIFDFVVVILS
IVGMFLAEMIEKYSVSPTLFRVIRLARIGRILRLIKGAKGIRTLLFALMMSLPALFNIGLLLFL
VMFIYAIFGMSNFAYVKKEAGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILNSAPPDCDP
DTIHPGSSVKGDRGDPSVGIFFFVSYIIISFLVVVNMYIAVILENFSVATEESAEPLSEDDFEM
FYEVWEKFDPDATQFIEFSKLSDFAAALDPPLLIAKPNKVQLIAMDLPMVSGDRIHCLDILFAF
TKRVLCESGEMDALRIQMEDRFMASNPSKVSYEPITTTLKRKQEEVSAAIIQRNFRCYLLKQRL
KNISSNYNKEAIKGRIDLPIKQDMIIDKLNGNSTPEKTDGSSSTTPPPSYDSVTKPDKEKFEKD
KPEKESKGKEVRENQK
```

Section 1

```
                      (1)  1        10        20        30             48
ClareAJ251507         (1)  ------------------------------------------------
huNalll18 (AK)        (1)  ------------------------------------------------
JeongAF225987         (1)  AGCGAAGCGGAGGCATAAGCAGAGAGGATTCTGGAAAGGTCTCTTTGT
Consensus             (1)
```

Section 2

```
                     (49)  49         60        70        80             96
ClareAJ251507         (1)  ------------------------------------------------
huNalll18 (AK)        (1)  ------------------------------------------------
JeongAF225987        (49)  TTTCTTATCCACAGAGAAGAAAGAAAAAAAATTGTAACTAATTTGTA
Consensus            (49)
```

Section 3

```
                     (97)  97          110       120        130          144
ClareAJ251507         (1)  ------------------------------------------------
huNalll18 (AK)        (1)  ------------------------------------------------
JeongAF225987        (97)  AACCTCTGTGGTCAAAAAAAAAAAAAAAAAAAAGCTGAACAGCTGCC
Consensus            (97)
```

Section 4

```
                    (145)  145   150          160         170        180    192
ClareAJ251507         (1)  ----------------TACCCTAACCATCTTGGATGCTGGGCTTTGTT
huNalll18 (AK)        (1)  ------------------------------------------------
JeongAF225987       (145)  AGAGGAAGACACGTTATACCCTAACCATCTTGGATGCTGGGCTTTGTT
Consensus           (145)                 TACCCTAACCATCTTGGATGCTGGGCTTTGTT
```

Section 5

```
                    (193)  193     200       210       220       230     240
ClareAJ251507        (33)  ATGCTGTAATTCATAAGGCTCTGTTTTATCAGAGATTATGGAGCAAGA
huNalll18 (AK)        (1)  ------------------------------------------------
JeongAF225987       (193)  ATGCTGTAATTCATAAGGCTCTGTTTTATCAGAGATTATGGAGCAAGA
Consensus           (193)  ATGCTGTAATTCATAAGGCTCTGTTTTATCAGAGATTATGGAGCAAGA
```

Section 6

```
                    (241)  241      250       260       270            288
ClareAJ251507        (81)  AAACTGAAGCCAAGCCACATCAAGGTTTGACAGGGATGAGATACCTGT
huNalll18 (AK)        (1)  ------------------------------------------------
JeongAF225987       (241)  AAACTGAAGCCAAGCCACATCAAGGTTTGACAGGGATGAGATACCTGT
Consensus           (241)  AAACTGAAGCCAAGCCACATCAAGGTTTGACAGGGATGAGATACCTGT
```

Section 7

```
                    (289)  289        300       310       320           336
ClareAJ251507       (129)  CAAGGATTCATAGTAGAGTGGCTTACTGGGAAAGGAGCAAAGAATCTC
huNalll18 (AK)        (1)  ------------------------------------------------
JeongAF225987       (289)  CAAGGATTCATAGTAGAGTGGCTTACTGGGAAAGGAGCAAAGAATCTC
Consensus           (289)  CAAGGATTCATAGTAGAGTGGCTTACTGGGAAAGGAGCAAAGAATCTC
```

```
                                                                    Section 8
              (337) 337          350         360         370          384
ClareAJ251507 (177) TTCTAGGGATATTGTAAGAATAAATGAGATAATTCACAGAAGGGACCT
huNaIII18 (AK)   (1) -----------------------------------------------
JeongAF225987 (337) TTCTAGGGATATTGTAAGAATAAATGAGATAATTCACAGAAGGGACCT
Consensus     (337) TTCTAGGGATATTGTAAGAATAAATGAGATAATTCACAGAAGGGACCT
                                                                    Section 9
              (385) 385   390        400         410        420       432
ClareAJ251507 (225) GGAGCTTTTCCGGAAAAAGGTGCTGTGACTATCTAAGGTAATTCGTAT
huNaIII18 (AK)   (1) -----------------------------------------------
JeongAF225987 (385) GGAGCTTTTCCGGAAAAAGGTGCTGTGACTATCTAAGGTAATTCGTAT
Consensus     (385) GGAGCTTTTCCGGAAAAAGGTGCTGTGACTATCTAAGGTAATTCGTAT
                                                                    Section 10
              (433) 433    440        450        460       470       480
ClareAJ251507 (273) GCAAGAAGCTACACGTAATTAAATGTGCAGGATGAAAAGATGGCACAG
huNaIII18 (AK)   (1) --------------------------------TGAAAAGATGGCACAG
JeongAF225987 (433) GCAAGAAGCTACACGTAATTAAATGTGCAGGATGAAAAGATGGCACAG
Consensus     (433) GCAAGAAGCTACACGTAATTAAATGTGCAGGATGAAAAGATGGCACAG
                                                                    Section 11
              (481) 481     490        500         510             528
ClareAJ251507 (321) GCACTGTTGGTACCCCCAGGACCTGAAAGCTTCCGCCTTTTTACTAGA
huNaIII18 (AK)  (17) GCACTGTTGGTACCCCCAGGACCTGAAAGCTTCCGCCTTTTTACTAGA
JeongAF225987 (481) GCACTGTTGGTACCCCCAGGACCTGAAAGCTTCCGCCTTTTTACTAGA
Consensus     (481) GCACTGTTGGTACCCCCAGGACCTGAAAGCTTCCGCCTTTTTACTAGA
                                                                    Section 12
              (529) 529        540        550        560          576
ClareAJ251507 (369) GAATCTCTTGCTGCTATCGAAAAACGTGCTGCAGAAGAGAAAGCCAAG
huNaIII18 (AK)  (65) GAATCTCTTGCTGCTATCGAAAAACGTGCTGCAGAAGAGAAAGCCAAG
JeongAF225987 (529) GAATCTCTTGCTGCTATCGAAAAACGTGCTGCAGAAGAGAAAGCCAAG
Consensus     (529) GAATCTCTTGCTGCTATCGAAAAACGTGCTGCAGAAGAGAAAGCCAAG
                                                                    Section 13
              (577) 577          590        600         610          624
ClareAJ251507 (417) AAGCCCAAAAAGGAACAAGATAATGATGATGAGAACAAACCAAAGCCA
huNaIII18 (AK) (113) AAGCCCAAAAAGGAACAAGATAATGATGATGAGAACAAACCAAAGCCA
JeongAF225987 (577) AAGCCCAAAAAGGAACAAGATAATGATGATGAGAACAAACCAAAGCCA
Consensus     (577) AAGCCCAAAAAGGAACAAGATAATGATGATGAGAACAAACCAAAGCCA
                                                                    Section 14
              (625) 625   630        640        650          660      672
ClareAJ251507 (465) AATAGTGACTTGGAAGCTGGAAGAACCTTCCATTTATTTATGGAGAC
huNaIII18 (AK) (161) AATAGTGACTTGGAAGCTGGAAGAACCTTCCATTTATTTATGGAGAC
JeongAF225987 (625) AATAGTGACTTGGAAGCTGGAAGAACCTTCCATTTATTTATGGAGAC
Consensus     (625) AATAGTGACTTGGAAGCTGGAAGAACCTTCCATTTATTTATGGAGAC
```

	(673)	673 680 690 700 710 720
ClareAJ251507	(513)	ATTCCTCCAGAGATGGTGTCAGAGCCCCTGGAGGACCTGGATCCCTAC
huNalll18 (AK)	(209)	ATTCCTCCAGAGATGGTGTCAGAGCCCCTGGAGGACCTGGATCCCTAC
JeongAF225987	(673)	ATTCCTCCAGAGATGGTGTCAGAGCCCCTGGAGGACCTGGATCCCTAC
Consensus	(673)	ATTCCTCCAGAGATGGTGTCAGAGCCCCTGGAGGACCTGGATCCCTAC

	(721)	721 730 740 750 768
ClareAJ251507	(561)	TATATCAATAAGAAAACTTTTATAGTAATGAATAAAGGAAAGGCAATT
huNalll18 (AK)	(257)	TATATCAATAAGAAAACTTTTATAGTAATGAATAAAGGAAAGGCAATT
JeongAF225987	(721)	TATATCAATAAGAAAACTTTTATAGTAATGAATAAAGGAAAGGCAATT
Consensus	(721)	TATATCAATAAGAAAACTTTTATAGTAATGAATAAAGGAAAGGCAATT

	(769)	769 780 790 800 816
ClareAJ251507	(609)	TTCCGATTCAGTGCCACCTCTGCCTTGTATATTTTAACTCCACTAAAC
huNalll18 (AK)	(305)	TTCCGATTCAGTGCCACCTCTGCCTTGTATATTTTAACTCCACTAAAC
JeongAF225987	(769)	TTCCGATTCAGTGCCACCTCTGCCTTGTATATTTTAACTCCACTAAAC
Consensus	(769)	TTCCGATTCAGTGCCACCTCTGCCTTGTATATTTTAACTCCACTAAAC

	(817)	817 830 840 850 864
ClareAJ251507	(657)	CCTGTTAGGAAAATTGCTATCAAGATTTTGGTACATTCTTTATTCAGC
huNalll18 (AK)	(353)	CCTGTTAGGAAAATTGCTATCAAGATTTTGGTACATTCTTTATTCAGC
JeongAF225987	(817)	CCTGTTAGGAAAATTGCTATCAAGATTTTGGTACATTCTTTATTCAGC
Consensus	(817)	CCTGTTAGGAAAATTGCTATCAAGATTTTGGTACATTCTTTATTCAGC

	(865)	865 870 880 890 900 912
ClareAJ251507	(705)	ATGCTTATCATGTGCACTATTTTGACCAACTGTGTATTTATGACCTTG
huNalll18 (AK)	(401)	ATGCTTATCATGTGCACTATTTTGACCAACTGTGTATTTATGACCTTG
JeongAF225987	(865)	ATGCTTATCATGTGCACTATTTTGACCAACTGTGTATTTATGACCTTG
Consensus	(865)	ATGCTTATCATGTGCACTATTTTGACCAACTGTGTATTTATGACCTTG

	(913)	913 920 930 940 950 960
ClareAJ251507	(753)	AGCAACCCTCCTGACTGGACAAAGAATGTAGAGTACACATTCACTGGA
huNalll18 (AK)	(449)	AGCAACCCTCCTGACTGGACAAAGAATGTAGAGTACACATTCACTGGA
JeongAF225987	(913)	AGCAACCCTCCTGACTGGACAAAGAATGTAGAGTACACATTCACTGGA
Consensus	(913)	AGCAACCCTCCTGACTGGACAAAGAATGTAGAGTACACATTCACTGGA

	(961)	961 970 980 990 1008
ClareAJ251507	(801)	ATCTATACCTTTGAGTCACTTATAAAAATCTTGGCAAGAGGGTTTTGC
huNalll18 (AK)	(497)	ATCTATACCTTTGAGTCACTTATAAAAATCTTGGCAAGAGGGTTTTGC
JeongAF225987	(961)	ATCTATACCTTTGAGTCACTTATAAAAATCTTGGCAAGAGGGTTTTGC
Consensus	(961)	ATCTATACCTTTGAGTCACTTATAAAAATCTTGGCAAGAGGGTTTTGC

```
                                                                  ——— Section 22
                (1009) 1009          ,1020          ,1030          ,1040              1056
ClareAJ251507   (849) TTAGAAGATTTTACGTTTCTTCGTGATCCATGGAACTGGCTGGATTTC
huNaIII18 (AK)  (545) TTAGAAGATTTTACGTTTCTTCGTGATCCATGGAACTGGCTGGATTTC
JeongAF225987  (1009) TTAGAAGATTTTACGTTTCTTCGTGATCCATGGAACTGGCTGGATTTC
Consensus      (1009) TTAGAAGATTTTACGTTTCTTCGTGATCCATGGAACTGGCTGGATTTC
                                                                  ——— Section 23
                (1057) 1057          ,1070          ,1080          ,1090              1104
ClareAJ251507   (897) AGTGTCATTGTGATGGCGTATGTAACAGAATTTGTAAGCCTAGGCAAT
huNaIII18 (AK)  (593) AGTGTCATTGTGATGGCGTATGTAACAGAATTTGTAAGCCTAGGCAAT
JeongAF225987  (1057) AGTGTCATTGTGATGGCATATGTGACAGAGTTTGTGGACCTGGGCAAT
Consensus      (1057) AGTGTCATTGTGATGGCGTATGTAACAGAATTTGTAAGCCTAGGCAAT
                                                                  ——— Section 24
                (1105) 1105  ,1110          ,1120          ,1130          1140         1152
ClareAJ251507   (945) GTTTCAGCCCTTCGAACTTTCAGAGTCTTGAGAGCCCTGAAAACTATT
huNaIII18 (AK)  (641) GTTTCAGCCCTTCGAACTTTCAGAGTCTTGAGAGCCCTGAAAACTATT
JeongAF225987  (1105) GTCTCAGCGTTGAGAACATTCAGAGTTCTCCGAGCACTGAAAACAATT
Consensus      (1105) GTTTCAGCCCTTCGAACTTTCAGAGTCTTGAGAGCTCTGAAAACTATT
                                                                  ——— Section 25
                (1153) 1153  ,1160          ,1170          ,1180          ,1190         1200
ClareAJ251507   (993) TCTGTAATTCCAGGTTTAAAGACCATTGTGGGGGCCCTGATCCAGTCG
huNaIII18 (AK)  (689) TCTGTAATTCCAGGTTTAAAGACCATTGTGGGGGCCCTGATCCAGTCG
JeongAF225987  (1153) TCAGTCATTCCAGGTTTAAAGACCATTGTGGGGGCCCTGATCCAGTCG
Consensus      (1153) TCTGTAATTCCAGGTTTAAAGACCATTGTGGGGGCCCTGATCCAGTCG
                                                                  ——— Section 26
                (1201) 1201          ,1210          ,1220          ,1230              1248
ClareAJ251507  (1041) GTAAAGAAGCTTTCTGATGTGATGATCCTGACTGTGTTCTGTCTGAGC
huNaIII18 (AK)  (737) GTAAAGAAGCTTTCTGATGTGATGATCCTGACTGTGTTCTGTCTGAGC
JeongAF225987  (1201) GTAAAGAAGCTTTCTGATGTGATGATCCTGACTGTGTTCTGTCTGAGC
Consensus      (1201) GTAAAGAAGCTTTCTGATGTGATGATCCTGACTGTGTTCTGTCTGAGC
                                                                  ——— Section 27
                (1249) 1249          ,1260          ,1270          ,1280              1296
ClareAJ251507  (1089) GTGTTTGCTCTCATTGGGCTGCAGCTGTTCATGGGCAATCTGAGGAAT
huNaIII18 (AK)  (785) GTGTTTGCTCTCATTGGGCTGCAGCTGTTCATGGGCAATCTGAGGAAT
JeongAF225987  (1249) GTGTTTGCTCTCATTGGGCTGCAGCTGTTCATGGGCAATCTGAGGAAT
Consensus      (1249) GTGTTTGCTCTCATTGGGCTGCAGCTGTTCATGGGCAATCTGAGGAAT
                                                                  ——— Section 28
                (1297) 1297          ,1310          ,1320          ,1330              1344
ClareAJ251507  (1137) AAATGTTTGCAGTGGCCCCCAAGCGATTCTGCTTTTGAAACCAACACC
huNaIII18 (AK)  (833) AAATGTTTGCAGTGGCCCCCAAGCGATTCTGCTTTTGAAACCAACACC
JeongAF225987  (1297) AAATGTTTGCAGTGGCCCCCAAGCGATTCTGCTTTTGAAACCAACACC
Consensus      (1297) AAATGTTTGCAGTGGCCCCCAAGCGATTCTGCTTTTGAAACCAACACC
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                                                                    —— Section 29
          (1345) 1345   ,1350        ,1360       ,1370      ,1380        1392
ClareAJ251507 (1185) ACTTCCTACTTTAATGGCACAATGGATTCAAATGGGACATTTGTTAAT
 huNaIII18 (AK)  (881) ACTTCCTACTTTAATGGCACAATGGATTCAAATGGGACATTTGTTAAT
JeongAF225987   (1345) ACTTCCTACTTTAATGGCACAATGGATTCAAATGGGACATTTGTTAAT
    Consensus (1345) ACTTCCTACTTTAATGGCACAATGGATTCAAATGGGACATTTGTTAAT
                                                                    —— Section 30
          (1393) 1393   ,1400       ,1410      ,1420       ,1430        1440
ClareAJ251507 (1233) GTAACAATGAGCACATTTAACTGGAAGGATTACATTGGAGATGACAGT
 huNaIII18 (AK)  (929) GTAACAATGAGCACATTTAACTGGAAGGATTACATTGGAGATGACAGT
JeongAF225987   (1393) GTAACAATGAGCACATTTAACTGGAAGGATTACATTGGAGATGACAGT
    Consensus (1393) GTAACAATGAGCACATTTAACTGGAAGGATTACATTGGAGATGACAGT
                                                                    —— Section 31
          (1441) 1441        ,1450       ,1460       ,1470            1488
ClareAJ251507 (1281) CACTTTTATGTTTTGGATGGGCAAAAAGACCCTTTACTCTGTGGAAAT
 huNaIII18 (AK)  (977) CACTTTTATGTTTTGGATGGGCAAAAAGACCCTTTACTCTGTGGAAAT
JeongAF225987   (1441) CACTTTTATGTTTTGGATGGGCAAAAAGACCCTTTACTCTGTGGAAAT
    Consensus (1441) CACTTTTATGTTTTGGATGGGCAAAAAGACCCTTTACTCTGTGGAAAT
                                                                    —— Section 32
          (1489) 1489        ,1500       ,1510       ,1520            1536
ClareAJ251507 (1329) GGCTCAGATGCAGGCCAGTGTCCAGAAGGATACATCTGTGTGAAGGCT
 huNaIII18 (AK) (1025) GGCTCAGATGCAGGCCAGTGTCCAGAAGGATACATCTGTGTGAAGGCT
JeongAF225987   (1489) GGCTCAGATGCAGGCCAGTGTCCAGAAGGATACATCTGTGTGAAGGCT
    Consensus (1489) GGCTCAGATGCAGGCCAGTGTCCAGAAGGATACATCTGTGTGAAGGCT
                                                                    —— Section 33
          (1537) 1537          ,1550       ,1560       ,1570          1584
ClareAJ251507 (1377) GGTCGAAACCCCAACTATGGCTACACAAGCTTTGACACCTTTAGCTGG
 huNaIII18 (AK) (1073) GGTCGAAACCCCAACTATGGCTACACAAGCTTTGACACCTTTAGCTGG
JeongAF225987   (1537) GGTCGAAACCCCAACTATGGCTACACAAGCTTTGACACCTTTAGCTGG
    Consensus (1537) GGTCGAAACCCCAACTATGGCTACACAAGCTTTGACACCTTTAGCTGG
                                                                    —— Section 34
          (1585) 1585   ,1590       ,1600       ,1610      ,1620        1632
ClareAJ251507 (1425) GCTTTCCTGTCTCTATTTCGACTCATGACTCAAGA TA TGGGAAAAT
 huNaIII18 (AK) (1121) GCTTTCCTGTCTCTATTTCGACTCATGACTCAAGATTA TGGGAAAAT
JeongAF225987   (1585) GCTTTCCTGTCTCTATTTCGACTCATGACTCAAGA TATTGGGAAAAT
    Consensus (1585) GCTTTCCTGTCTCTATTTCGACTCATGACTCAAGACTACTGGGAAAAT
                                                                    —— Section 35
          (1633) 1633   ,1640       ,1650       ,1660      ,1670        1680
ClareAJ251507 (1473) CTTTACCAGTTGACATTACGTGCTGCTGGGAAAACATACATGATATTT
 huNaIII18 (AK) (1169) CTTTACCAGTTGACATTACGTGCTGCTGGGAAAACATACATGATATTT
JeongAF225987   (1633) CTTTACCAGTTGACATTACGTGCTGCTGGGAAAACATACATGATATTT
    Consensus (1633) CTTTACCAGTTGACATTACGTGCTGCTGGGAAAACATACATGATATTT
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                                                              ———— Section 36
              (1681) 1681       ,1690      ,1700      ,1710        1728
ClareAJ251507 (1521) TTTGTCCTGGTCATTTTCTTGGGCTCATTTTATTTGGTGAATTTGATC
 huNaIII18 (AK) (1217) TTTGTCCTGGTCATTTTCTTGGGCTCATTTTATTTGGTGAATTTGATC
JeongAF225987  (1681) TTTGTCCTGGTCATTTTCTTGGGCTCATTTTATTTGGTGAATTTGATC
    Consensus (1681) TTTGTCCTGGTCATTTTCTTGGGCTCATTTTATTTGGTGAATTTGATC
                                                              ———— Section 37
              (1729) 1729       ,1740      ,1750      ,1760        1776
ClareAJ251507 (1569) CTGGCTGTGGTGGCCATGGCCTATGAGGAGCAGAATCAGGCCACCTTG
 huNaIII18 (AK) (1265) CTGGCTGTGGTGGCCATGGCCTATGAGGAGCAGAATCAGGCCACCTTG
JeongAF225987  (1729) CTGGCTGTGGTGGCCATGGCCTATGAGGAGCAGAATCAGGCCACCTTG
    Consensus (1729) CTGGCTGTGGTGGCCATGGCCTATGAGGAGCAGAATCAGGCCACCTTG
                                                              ———— Section 38
              (1777) 1777       ,1790      ,1800      ,1810        1824
ClareAJ251507 (1617) GAAGAAGCAGAACAAAAGAGGCCGAATTTCAGCAGATGCTCGAACAG
 huNaIII18 (AK) (1313) GAAGAAGCAGAACAAAAGAGGCCGAATTTCAGCAGATGCTCGAACAG
JeongAF225987  (1777) GAAGAAGCAGAACAAAAGAGGCCGAATTTCAGCAGATGCTCGAACAG
    Consensus (1777) GAAGAAGCAGAACAAAAGAGGCCGAATTTCAGCAGATGCTCGAACAG
                                                              ———— Section 39
              (1825) 1825  ,1830      ,1840      ,1850      ,1860   1872
ClareAJ251507 (1665) CTTAAAAAGCAACAGGAAGAAGCTCAGGCAGTTGCGGCAGCATCAGCT
 huNaIII18 (AK) (1361) CTTAAAAAGCAACAGGAAGAAGCTCAGGCAGTTGCGGCAGCATCAGCT
JeongAF225987  (1825) CTTAAAAAGCAACAGGAAGAAGCTCAGGCAGTTGCGGCAGCATCAGCT
    Consensus (1825) CTTAAAAAGCAACAGGAAGAAGCTCAGGCAGTTGCGGCAGCATCAGCT
                                                              ———— Section 40
              (1873) 1873  ,1880      ,1890      ,1900      ,1910   1920
ClareAJ251507 (1713) GCTTCAAGAGATTTCAGTGGA TAGGTGGGTTAGGAGAGCTGTTGGAA
 huNaIII18 (AK) (1409) GCTTCAAGAGATTTCAGTGGA TAGGTGGGTTAGGAGAGCTGTTGGAA
JeongAF225987  (1873) GCTTCAAGAGATTTCAGTGGAGTAGGTGGGTTAGGAGAGCTGTTGGAA
    Consensus (1873) GCTTCAAGAGATTTCAGTGGAATAGGTGGGTTAGGAGAGCTGTTGGAA
                                                              ———— Section 41
              (1921) 1921       ,1930      ,1940      ,1950        1968
ClareAJ251507 (1761) AGTTCTTCAGAAGCATCAAAGTTGAGTTCCAAA GTGCTAAAGAATGG
 huNaIII18 (AK) (1457) AGTTCTTCAGAAGCATCAAAGTTGAGTTCCAAA GTGCTAAAGAATGG
JeongAF225987  (1921) AGTTCTTCAGAAGCATCAAAGTTGAGTTCCAAAGGTGCTAAAGAATGG
    Consensus (1921) AGTTCTTCAGAAGCATCAAAGTTGAGTTCCAAAAGTGCTAAAGAATGG
                                                              ———— Section 42
              (1969) 1969       ,1980      ,1990       2000        2016
ClareAJ251507 (1809) AGGAACCG AGGAAGAAAAGAAGAC GAGAGAGCACCTTGAAGGAAAC
 huNaIII18 (AK) (1505) AGGAACCG AGGAAGAAAAGAAGACGGAGAGAGCACCTTGAAGGAAAC
JeongAF225987  (1969) AGGAACCGGAGGAAGAAAAGAAGAC GAGAGAGCACCTTGAAGGAAAC
    Consensus (1969) AGGAACCGAGGAAGAAAAGAAGACAGAGAGAGCACCTTGAAGGAAAC
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—————————————————————————————————————— Section 43

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                  (2017) 2017              2030          2040          2050          2064
    ClareAJ251507 (1857) AACAAAGGAGAGAGAGACAGCTTTCCCAAATCCGAATCTGAAGACAGC
    huNalll18 (AK) (1553) AACAAAGGAGAGAGAGACAGCTTTCCCAAATCCGAATCTGAAGACAGC
JeongAF225987    (2017) AACAAAGGAGAGAGAGACAGCTTTCCCAAATCCGAATCTGAAGACAGC
    Consensus (2017) AACAAAGGAGAGAGAGACAGCTTTCCCAAATCCGAATCTGAAGACAGC
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—————————————————————————————————————— Section 44

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                  (2065) 2065   2070          2080          2090          2100       2112
    ClareAJ251507 (1905) GTCAAAGAAGCAGCTTCCTTTTCTCCATGGATGGAAACAGACTGACC
    huNalll18 (AK) (1601) GTCAAAGAAGCAGCTTCCTTTTCTCCATGGATGGAAACAGACTGACC
JeongAF225987    (2065) GTCAAAGAAGCAGCTTCCTTTTCTCCATGGATGGAAACAGACTGACC
    Consensus (2065) GTCAAAGAAGCAGCTTCCTTTTCTCCATGGATGGAAACAGACTGACC
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—————————————————————————————————————— Section 45

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                  (2113) 2113    2120          2130          2140          2150       2160
    ClareAJ251507 (1953) AGTGACAAAAAATTCTGCTCCCCTCATCAGTCTCTCTTGAGTATCCGT
    huNalll18 (AK) (1649) AGTGACAAAAAATTCTGCTCCCCTCATCAGTCTCTCTTGAGTATCCGT
JeongAF225987    (2113) AGTGACAAAAAATTCTGCTCCCCTCATCAGTCTCTCTTGAGTATCCGT
    Consensus (2113) AGTGACAAAAAATTCTGCTCCCCTCATCAGTCTCTCTTGAGTATCCGT
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—————————————————————————————————————— Section 46

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                  (2161) 2161         2170          2180          2190          2208
    ClareAJ251507 (2001) GGCTCCCTGTTTTCCCCAAGACGCAATAGCAAAACAAGCATTTTCAGT
    huNalll18 (AK) (1697) GGCTCCCTGTTTTCCCCAAGACGCAATAGCAAAACAAGCATTTTCAGT
JeongAF225987    (2161) GGCTCCCTGTTTTCCCCAAGACGCAATAGCAAAACAAGCATTTTCAGT
    Consensus (2161) GGCTCCCTGTTTTCCCCAAGACGCAATAGCAAAACAAGCATTTTCAGT
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—————————————————————————————————————— Section 47

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                  (2209) 2209          2220          2230          2240          2256
    ClareAJ251507 (2049) TTCAGAGGTCGGGCAAAGGATGTTGGATCTGAAAATGACTTTGCTGAT
    huNalll18 (AK) (1745) TTCAGAGGTCGGGCAAAGGATGTTGGATCTGAAAATGACTTTGCTGAT
JeongAF225987    (2209) TTCAGAGGTCGGGCAAAGGATGTTGGATCTGAAAATGACTTTGCTGAT
    Consensus (2209) TTCAGAGGTCGGGCAAAGGATGTTGGATCTGAAAATGACTTTGCTGAT
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—————————————————————————————————————— Section 48

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                  (2257) 2257          2270          2280          2290          2304
    ClareAJ251507 (2097) GATGAACACAGCACATTTGAAGACAGCGAAAGCAGGAGAGACTCACTG
    huNalll18 (AK) (1793) GATGAACACAGCACATTTGAAGACAGCGAAAGCAGGAGAGACTCACTG
JeongAF225987    (2257) GATGAACACAGCACATTTGAAGACGGCGAAAGCAGGAGAGACTCACTG
    Consensus (2257) GATGAACACAGCACATTTGAAGACAGCGAAAGCAGGAGAGACTCACTG
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—————————————————————————————————————— Section 49

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                  (2305) 2305   2310          2320          2330          2340       2352
    ClareAJ251507 (2145) TTTGTGCCGCACAGACATGGAGAGCGACGCAACAGTAACG---------
    huNalll18 (AK) (1841) TTTGTGCCGCACAGACATGGAGAGCGACGCAACAGTAACGTTAGTCAG
JeongAF225987    (2305) TTTGTGCCGCACAGACATGGAGAGCGACGCAACAGTAACGTTAGTCAG
    Consensus (2305) TTTGTGCCGCACAGACATGGAGAGCGACGCAACAGTAACGTTAGTCAG
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                                                                    Section 50
               (2353) 2353      2360       2370       2380       2390       2400
ClareAJ251507 (2185) --------------------------------------------------------
huNaIII18 (AK) (1889) GCCAGTATGTCATCCAGGATGGTGCCAGGGCTTCCAGCAAATGGGAAG
JeongAF225987  (2353) GCCAGTATGTCATCCAGGATGGTGCCAGGGCTTCCAGCAAATGGGAAG
   Consensus  (2353) GCCAGTATGTCATCCAGGATGGTGCCAGGGCTTCCAGCAAATGGGAAG
                                                                    Section 51
               (2401) 2401       2410       2420       2430           2448
ClareAJ251507 (2185) ------------------------------------------------
huNaIII18 (AK) (1937) ATGCACAGCACTGTGGATTGCAATGGTGTGGTTTCCTTGGTGGGTGGA
JeongAF225987  (2401) ATGCACAGCACTGTGGATTGCAATGGTGTGGTTTCCTTGGTGGGTGGA
   Consensus  (2401) ATGCACAGCACTGTGGATTGCAATGGTGTGGTTTCCTTGGTGGGTGGA
                                                                    Section 52
               (2449) 2449       2460       2470       2480           2496
ClareAJ251507 (2185) -----------------------------------------------GCACC
huNaIII18 (AK) (1985) CCTTCAGCTCTAACGTCACCTACTGGACAACTTCCCCCAGAGGGCACC
JeongAF225987  (2449) CCTTCAGCTCTAACGTCACCTACTGGACAACTTCCCCCAGAGGGCACC
   Consensus  (2449) CCTTCAGCTCTAACGTCACCTACTGGACAACTTCCCCCAGAGGGCACC
                                                                    Section 53
               (2497) 2497         2510       2520       2530           2544
ClareAJ251507 (2190) ACCACTGAAACGGAAGTCAGAAAGAGAAGGTTAAGCTCTTACCAGATT
huNaIII18 (AK) (2033) ACCACAGAAACGGAAGTCAGAAAGAGAAGGTTAAGCTCTTACCAGATT
JeongAF225987  (2497) ACCACTGAAACGGAAGTCAGAAAGAGAAGGTTAAGCTCTTACCAGATT
   Consensus  (2497) ACCAC.GAAACGGAAGTCAGAAAGAGAAGGTTAAGCTCTTACCAGATT
                                                                    Section 54
               (2545) 2545  2550       2560       2570       2580       2592
ClareAJ251507 (2238) TCAATGGAGATGCTGGAGGATTCCTCTGGAAGGCAAAGAGCCGTGAGC
huNaIII18 (AK) (2081) TCAATGGAGATGCTGGAGGATTCCTCTGGAAGGCAAAGAGCCGTGAGC
JeongAF225987  (2545) TCAATGGAGATGCTGGAGGATTCCTCTGGAAGGCAAAGAGCCGTGAGC
   Consensus  (2545) TCAATGGAGATGCTGGAGGATTCCTCTGGAAGGCAAAGAGCCGTGAGC
                                                                    Section 55
               (2593) 2593  2600       2610       2620       2630       2640
ClareAJ251507 (2286) ATAGCCAGCATTCTGACCAACACAATGGAAGAACTTGAAGAATCTAGA
huNaIII18 (AK) (2129) ATAGCCAGCATTCTGACCAACACAATGGAAGAACTTGAAGAATCTAGA
JeongAF225987  (2593) ATAGCCAGCATTCTGACCAACACAATGGAAGAACTTGAAGAATCTAGA
   Consensus  (2593) ATAGCCAGCATTCTGACCAACACAATGGAAGAACTTGAAGAATCTAGA
                                                                    Section 56
               (2641) 2641       2650       2660       2670           2688
ClareAJ251507 (2334) CAGAAATGTCCGCCATGCTGGTATAGATTTGCCAATGTGTTCTTGATC
huNaIII18 (AK) (2177) CAGAAATGTCCGCCATGCTGGTATAGATTTGCCAATGTGTTCTTGATC
JeongAF225987  (2641) CAGAAATGTCCGCCATGCTGGTATAGATTTGCCAATGTGTTCTTGATC
   Consensus  (2641) CAGAAATGTCCGCCATGCTGGTATAGATTTGCCAATGTGTTCTTGATC
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                                                                      Section 57
           (2689) 2689              2700        2710        2720            2736
ClareAJ251507 (2382) TGGGACTGCTGTGATGCATGGTTAAAAGTAAAACATCTTGTGAATTTA
huNalII18 (AK) (2225) TGGGACTGCTGTGATGCATGGTTAAAAGTAAAACATCTTGTGAATTTA
JeongAF225987 (2689) TGGGACTGCTGTGATGCATGGTTAAAAGTAAAACATCTTGTGAATTTA
    Consensus (2689) TGGGACTGCTGTGATGCATGGTTAAAAGTAAAACATCTTGTGAATTTA
                                                                      Section 58
           (2737) 2737              2750        2760        2770            2784
ClareAJ251507 (2430) ATTGTTATGGATCCATTTGTTGATCTTGCCATCACTATTTGCATTGTC
huNalII18 (AK) (2273) ATTGTTATGGATCCATTTGTTGATCTTGCCATCACTATTTGCATTGTC
JeongAF225987 (2737) ATTGTTATGGATCCATTTGTTGATCTTGCCATCACTATTTGCATTGTC
    Consensus (2737) ATTGTTATGGATCCATTTGTTGATCTTGCCATCACTATTTGCATTGTC
                                                                      Section 59
           (2785) 2785   2790        2800        2810        2820            2832
ClareAJ251507 (2478) TTAAATACCCTCTTTATGGCCATGGAGCACTACCCATGACTGAGCAA
huNalII18 (AK) (2321) TTAAATACCCTCTTTATGGCCATGGAGCACTACCCATGACTGAGCAA
JeongAF225987 (2785) TTAAATACCCTCTTTATGGCCATGGAGCACTACCCATGACTGAGCAA
    Consensus (2785) TTAAATACCCTCTTTATGGCCATGGAGCACTACCCATGACTGAGCAA
                                                                      Section 60
           (2833) 2833   2840        2850        2860        2870            2880
ClareAJ251507 (2526) TTCAGTAGTGTGTTGACTGTAGGAAACCTGGTCTTTACTGGGATTTTC
huNalII18 (AK) (2369) TTCAGTAGTGTGTTGACTGTAGGAAACCTGGTCTTTACTGGGATTTTC
JeongAF225987 (2833) TTCAGTAGTGTGTTGACTGTAGGAAACCTGGTCTTTACTGGGATTTTC
    Consensus (2833) TTCAGTAGTGTGTTGACTGTAGGAAACCTGGTCTTTACTGGGATTTTC
                                                                      Section 61
           (2881) 2881   2890        2900        2910                      2928
ClareAJ251507 (2574) ACAGCAGAAATGGTTCTCAAGATCATTGCCATGGATCCTTATTACTAT
huNalII18 (AK) (2417) ACAGCAGAAATGGTTCTCAAGATCATTGCCATGGATCCTTATTACTAT
JeongAF225987 (2881) ACAGCAGAAATGGTTCTCAAGATCATTGCCATGGATCCTTATTACTAT
    Consensus (2881) ACAGCAGAAATGGTTCTCAAGATCATTGCCATGGATCCTTATTACTAT
                                                                      Section 62
           (2929) 2929        2940        2950        2960            2976
ClareAJ251507 (2622) TTCCAAGAAGGCTGGAATATCTTTGATGGAATTATTGTCAGCCTCAGT
huNalII18 (AK) (2465) TTCCAAGAAGGCTGGAATATCTTTGATGGAATTATTGTCAGCCTCAGT
JeongAF225987 (2929) TTCCAAGAAGGCTGGAATATCTTTGATGGAATTATTGTCAGCCTCAGT
    Consensus (2929) TTCCAAGAAGGCTGGAATATCTTTGATGGAATTATTGTCAGCCTCAGT
                                                                      Section 63
           (2977) 2977              2990        3000        3010            3024
ClareAJ251507 (2670) TTAATGGAGCTTGGTCTGTCAAATGTGGAGGGATTGTCTGTACTGCGA
huNalII18 (AK) (2513) TTAATGGAGCTTGGTCTGTCAAATGTGGAGGGATTGTCTGTACTGCGA
JeongAF225987 (2977) TTAATGGAGCTTGGTCTGTCAAATGTGGAGGGATTGTCTGTACTGCGA
    Consensus (2977) TTAATGGAGCTTGGTCTGTCAAATGTGGAGGGATTGTCTGTACTGCGA
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—— Section 64

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                    (3025) 3025    3030        3040        ,3050       3060        3072
ClareAJ251507 (2718) TCATTCAGACTGCTTAGAGTTTTCAAGTTGGCAAAATCCTGGCCCACA
huNalll18 (AK) (2561) TCATTCAGACTGCTTAGAGTTTTCAAGTTGGCAAAATCCTGGCCCACA
JeongAF225987  (3025) TCATTCAGACTGCTTAGAGTTTTCAAGTTGGCAAAATCCTGGCCCACA
Consensus (3025) TCATTCAGACTGCTTAGAGTTTTCAAGTTGGCAAAATCCTGGCCCACA
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—— Section 65

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                    (3073) 3073    3080        3090        3100        3110        3120
ClareAJ251507 (2766) CTAAATATGCTAATTAAGATCATTGGCAATTCTGTGGGGGCTCTAGGA
huNalll18 (AK) (2609) CTAAATATGCTAATTAAGATCATTGGCAATTCTGTGGGGGCTCTAGGA
JeongAF225987  (3073) CTAAATATGCTAATTAAGATCATTGGCAATTCTGTGGGGGCTCTAGGA
Consensus (3073) CTAAATATGCTAATTAAGATCATTGGCAATTCTGTGGGGGCTCTAGGA
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—— Section 66

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                    (3121) 3121    ,3130       3140        ,3150                   3168
ClareAJ251507 (2814) AACCTCACCTTGGTGTTGGCCATCATCGTCTTCATTTTTGCTGTGGTC
huNalll18 (AK) (2657) AACCTCACCTTGGTGTTGGCCATCATCGTCTTCATTTTTGCTGTGGTC
JeongAF225987  (3121) AACCTCACCTTGGTGTTGGCCATCATCGTCTTCATTTTTGCTGTGGTC
Consensus (3121) AACCTCACCTTGGTGTTGGCCATCATCGTCTTCATTTTTGCTGTGGTC
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—— Section 67

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                    (3169) 3169    ,3180       ,3190       ,3200       3216
ClareAJ251507 (2862) GGCATGCAGCTCTTTGGTAAGAGCTACAAAGAATGTGTCTGCAAGATC
huNalll18 (AK) (2705) GGCATGCAGCTCTTTGGTAAGAGCTACAAAGAATGTGTCTGCAAGATC
JeongAF225987  (3169) GGCATGCAGCTCTTTGGTAAGAGCTACAAAGAATGTGTCTGCAAGATC
Consensus (3169) GGCATGCAGCTCTTTGGTAAGAGCTACAAAGAATGTGTCTGCAAGATC
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—— Section 68

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                    (3217) 3217            ,3230       ,3240       3250        3264
ClareAJ251507 (2910) AATGATGACTGTACGCTCCCACGGTGGCACATGAACGACTTCTTCCAC
huNalll18 (AK) (2753) AATGATGACTGTACGCTCCCACGGTGGCACATGAACGACTTCTTCCAC
JeongAF225987  (3217) AATGATGACTGTACGCTCCCACGGTGGCACATGAACGACTTCTTCCAC
Consensus (3217) AATGATGACTGTACGCTCCCACGGTGGCACATGAACGACTTCTTCCAC
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—— Section 69

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                    (3265) 3265    3270        3280        ,3290       3300        3312
ClareAJ251507 (2958) TCCTTCCTGATTGTGTTCCGCGTGCTGTGTGGAGAGTGGATAGAGACC
huNalll18 (AK) (2801) TCCTTCCTGATTGTGTTCCGCGTGCTGTGTGGAGAGTGGATAGAGACC
JeongAF225987  (3265) TCCTTCCTGATTGTGTTCCGCGTGCTGTGTGGAGAGTGGATAGAGACC
Consensus (3265) TCCTTCCTGATTGTGTTCCGCGTGCTGTGTGGAGAGTGGATAGAGACC
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—— Section 70

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                    (3313) 3313    3320        3330        ,3340       ,3350       3360
ClareAJ251507 (3006) ATGTGGGACTGTATGGAGGTCGCTGGCCAAACCATGTGCCTTATTGTT
huNalll18 (AK) (2849) ATGTGGGACTGTATGGAGGTCGCTGGCCAAACCATGTGCCTTATTGTT
JeongAF225987  (3313) ATGTGGGACTGTATGGAGGTCGCTGGCCAAACCATGTGCCTTATTGTT
Consensus (3313) ATGTGGGACTGTATGGAGGTCGCTGGCCAAACCATGTGCCTTATTGTT
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                                                                    ─── Section 71
           (3361) 3361          3370          3380          3390              3408
ClareAJ251507 (3054) TTCATGTTGGTCATGGTCATTGGAAACCTTGTGGTTCTGAACCTCTTT
 huNalll18 (AK) (2897) TTCATGTTGGTCATGGTCATTGGAAACCTTGTGGTTCTGAACCTCTTT
JeongAF225987  (3361) TTCATGTTGGTCATGGTCATTGGAAACCTTGTGGTTCTGAACCTCTTT
    Consensus (3361) TTCATGTTGGTCATGGTCATTGGAAACCTTGTGGTTCTGAACCTCTTT
                                                                    ─── Section 72
           (3409) 3409          3420          3430          3440              3456
ClareAJ251507 (3102) CTGGCCTTATTGTTGAGTTCATTTAGCTCAGACAACCTTGCTGCTACT
 huNalll18 (AK) (2945) CTGGCCTTATTGTTGAGTTCATTTAGCTCAGACAACCTTGCTGCTACT
JeongAF225987  (3409) CTGGCCTTATTATTGAGTTCATTTAGCTCAGACAACCTTGCTGCTACT
    Consensus (3409) CTGGCCTTATTGTTGAGTTCATTTAGCTCAGACAACCTTGCTGCTACT
                                                                    ─── Section 73
           (3457) 3457          3470          3480          3490              3504
ClareAJ251507 (3150) GATGATGACAATGAAATGAATAATCTGCAGATTGCAGTAGGAAGAATG
 huNalll18 (AK) (2993) GATGATGACAATGAAATGAATAATCTGCAGATTGCAGTAGGAAGAATG
JeongAF225987  (3457) GATGATGACAATGAAATGAATAATCTGCAGATTGCAGTAGGAAGAATG
    Consensus (3457) GATGATGACAATGAAATGAATAATCTGCAGATTGCAGTAGGAAGAATG
                                                                    ─── Section 74
           (3505) 3505  3510          3520          3530          3540        3552
ClareAJ251507 (3198) CAAAAGGGAATTGATTATGTGAAAAATAAGATGCGGGAGTGTTTCCAA
 huNalll18 (AK) (3041) CAAAAGGGAATTGATTATGTGAAAAATAAGATGCGGGAGTGTTTCCAA
JeongAF225987  (3505) CAAAAGGGAATTGATTATGTGAAAAATAAGATGCGGGAGTGTTTCCAA
    Consensus (3505) CAAAAGGGAATTGATTATGTGAAAAATAAGATGCGGGAGTGTTTCCAA
                                                                    ─── Section 75
           (3553) 3553   3560          3570          3580          3590       3600
ClareAJ251507 (3246) AAAGCCTTTTTTAGAAAGCCAAAAGTTATAGAAATCCATGAAGGCAAT
 huNalll18 (AK) (3089) AAAGCCTTTTTTAGAAAGCCAAAAGTTATAGAAATCCATGAAGGCAAT
JeongAF225987  (3553) AAAGCCTTTTTTAGAAAGCCAAAAGTTATAGAAATCCATGAAGGCAAT
    Consensus (3553) AAAGCCTTTTTTAGAAAGCCAAAAGTTATAGAAATCCATGAAGGCAAT
                                                                    ─── Section 76
           (3601) 3601·         3610          3620          3630              3648
ClareAJ251507 (3294) AAGATAGACAGCTGCATGTCCAATAATACTGGAATTGAAATAAGCAAA
 huNalll18 (AK) (3137) AAGATAGACAGCTGCATGTCCAATAATACTGGAATTGAAATAAGCAAA
JeongAF225987  (3601) AAGATAGACAGCTGCATGTCCAATAATACTGGAATTGAAATAAGCAAA
    Consensus (3601) AAGATAGACAGCTGCATGTCCAATAATACTGGAATTGAAATAAGCAAA
                                                                    ─── Section 77
           (3649) 3649          3660          3670          3680              3696
ClareAJ251507 (3342) GAGCTTAATTATCTTAGAGATGGGAATGGAACCACCAGTGGTGTAGGT
 huNalll18 (AK) (3185) GAGCTTAATTATCTTAGAGATGGGAATGGAACCACCAGTGGTGTAGGT
JeongAF225987  (3649) GAGCTTAATTATCTTAGAGATGGGAATGGAACCACCAGTGGTGTAGGT
    Consensus (3649) GAGCTTAATTATCTTAGAGATGGGAATGGAACCACCAGTGGTGTAGGT
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                                                               ———————————————— Section 78
                (3697) 3697            3710          3720          3730              3744
ClareAJ251507 (3390) ACTGGAAGCAGTGTTGAAAAATACGTAATCGATGAAAATGATTATATG
 huNaIII18 (AK) (3233) ACTGGAAGCAGTGTTGAAAAATACGTAATCGATGAAAATGATTATATG
JeongAF225987   (3697) ACTGGAAGCAGTGTTGAAAAATACGTAATCGATGAAAATGATTATATG
    Consensus (3697) ACTGGAAGCAGTGTTGAAAAATACGTAATCGATGAAAATGATTATATG
                                                               ———————————————— Section 79
                (3745) 3745  3750        3760         3770         3780              3792
ClareAJ251507 (3438) TCATTCATAAACAACCCCAGCCTCACCGTCACAGTGCCAATTGCTGTT
 huNaIII18 (AK) (3281) TCATTCATAAACAACCCCAGCCTCACCGTCACAGTGCCAATTGCTGTT
JeongAF225987   (3745) TCATTCATAAACAACCCCAGCCTCACCGTCACAGTGCCAATTGCTGTT
    Consensus (3745) TCATTCATAAACAACCCCAGCCTCACCGTCACAGTGCCAATTGCTGTT
                                                               ———————————————— Section 80
                (3793) 3793    3800         3810         3820          3830           3840
ClareAJ251507 (3486) GGAGAGTCTGACTTTGAAAACTTAAATACTGAAGAGTTCAGCAGTGAG
 huNaIII18 (AK) (3329) GGAGAGTCTGACTTTGAAAACTTAAATACTGAAGAGTTCAGCAGTGAG
JeongAF225987   (3793) GGAGAGTCTGACTTTGAAAACTTAAATACTGAAGAGTTCAGCAGTGAG
    Consensus (3793) GGAGAGTCTGACTTTGAAAACTTAAATACTGAAGAGTTCAGCAGTGAG
                                                               ———————————————— Section 81
                (3841) 3841     3850         3860         3870                       3888
ClareAJ251507 (3534) TCAGAACTAGAAGAAAGCAAGAGAAATTAAATGCAACCAGCTCATCT
 huNaIII18 (AK) (3377) TCAGAACTAGAAGAAAGCAAGAGAAATTAAATGCAACCAGCTCATCT
JeongAF225987   (3841) TCAGAACTAGAAGAAAGCAAGAGAAATTAAATGCAACCAGCTCATCT
    Consensus (3841) TCAGAACTAGAAGAAAGCAAGAGAAATTAAATGCAACCAGCTCATCT
                                                               ———————————————— Section 82
                (3889) 3889        3900         3910          3920                   3936
ClareAJ251507 (3582) GAAGGAAGCACAGTTGATGTTGTTCTACCCCGAGAAGGTGAACAAGCT
 huNaIII18 (AK) (3425) GAAGGAAGCACAGTTGATGTTGTTCTACCCCGAGAAGGTGAACAAGCT
JeongAF225987   (3889) GAAGGAAGCACAGTTGATGTTGTTCTACCCCGAGAAGGTGAACAAGCT
    Consensus (3889) GAAGGAAGCACAGTTGATGTTGTTCTACCCCGAGAAGGTGAACAAGCT
                                                               ———————————————— Section 83
                (3937) 3937           3950          3960         3970               3984
ClareAJ251507 (3630) GAAACTGAACCCGAAGAAGACCTTAAACCGGAAGCTTGTTTTACTGAA
 huNaIII18 (AK) (3473) GAAACTGAACCCGAAGAAGACCTTAAACCGGAAGCTTGTTTTACTGAA
JeongAF225987   (3937) GAAACTGAACCCGAAGAAGACTTTAAACCGGAAGCTTGTTTTACTGAA
    Consensus (3937) GAAACTGAACCCGAAGAAGACCTTAAACCGGAAGCTTGTTTTACTGAA
                                                               ———————————————— Section 84
                (3985) 3985   3990         4000          4010         4020           4032
ClareAJ251507 (3678) GGATGTATTAAAAGTTTCCATTCTGTCAAGTAAGTACAGAAGAAGGC
 huNaIII18 (AK) (3521) GGATGTATTAAAAGTTTCCATTCTGTCAAGTAAGTACAGAAGAAGGC
JeongAF225987   (3985) GGGTGTATTAAAAGTTTCCATTCTGTCAAGTAAGTACAGAAGAAGGC
    Consensus (3985) GGATGTATTAAAAGTTTCCATTCTGTCAAGTAAGTACAGAAGAAGGC
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                                                                              Section 85
                (4033) 4033        4040        4050        4060        4070        4080
ClareAJ251507 (3726) AAAGGGAAGATCTGGTGGAATCTTCGAAAAACCTGCTACAGTATTGTT
huNaIII18 (AK) (3569) AAAGGGAAGATCTGGTGGAATCTTCGAAAAACCTGCTACAGTATTGTT
JeongAF225987    (4033) AAAGGGAAGATCTGGTGGAATCTTCGAAAAACCTGCTACAGTATTGTT
Consensus (4033) AAAGGGAAGATCTGGTGGAATCTTCGAAAAACCTGCTACAGTATTGTT
                                                                              Section 86
                (4081) 4081        4090        4100        4110              4128
ClareAJ251507 (3774) GAGCACAACTGGTTTGAGACTTTCATTGTGTTCATGATCCTTCTCAGT
huNaIII18 (AK) (3617) GAGCACAACTGGTTTGAGACTTTCATTGTGTTCATGATCCTTCTCAGT
JeongAF225987    (4081) GAGCACAACTGGTTTGAGACTTTCATTGTGTTCATGATCCTTCTCAGT
Consensus (4081) GAGCACAACTGGTTTGAGACTTTCATTGTGTTCATGATCCTTCTCAGT
                                                                              Section 87
                (4129) 4129        4140        4150        4160              4176
ClareAJ251507 (3822) AGTGGTGCATTGGCCTTTGAAGATATATACATTGAACAGCGAAAGACT
huNaIII18 (AK) (3665) AGTGGTGCATTGGCCTTTGAAGATATATACATTGAACAGCGAAAGACT
JeongAF225987    (4129) AGTGGTGCATTGGCCTTTGAAGATATATACATTGAACAGCGAAAGACT
Consensus (4129) AGTGGTGCATTGGCCTTTGAAGATATATACATTGAACAGCGAAAGACT
                                                                              Section 88
                (4177) 4177        4190        4200        4210              4224
ClareAJ251507 (3870) ATCAAAACCATGCTAGAATATGCTGACAAAGTCTTTACCTATATATTC
huNaIII18 (AK) (3713) ATCAAAACCATGCTAGAATATGCTGACAAAGTCTTTACCTATATATTC
JeongAF225987    (4177) ATCAAAACCATGCTAGAATATGCTGACAAAGTCTTTACCTATATATTC
Consensus (4177) ATCAAAACCATGCTAGAATATGCTGACAAAGTCTTTACCTATATATTC
                                                                              Section 89
                (4225) 4225  4230        4240        4250        4260        4272
ClareAJ251507 (3918) ATTCTGGAAATGCTTCTCAAATGGGTTGCTTATGGATTTCAAACATAT
huNaIII18 (AK) (3761) ATTCTGGAAATGCTTCTCAAATGGGTTGCTTATGGATTTCAAACATAT
JeongAF225987    (4225) ATTCTGGAAATGCTTCTCAAATGGGTTGCTTATGGATTTCAAACATAT
Consensus (4225) ATTCTGGAAATGCTTCTCAAATGGGTTGCTTATGGATTTCAAACATAT
                                                                              Section 90
                (4273) 4273  4280        4290        4300        4310        4320
ClareAJ251507 (3966) TTCACTAATGCCTGGTGCTGGCTAGATTTCTTGATCGTTGATGTTTCT
huNaIII18 (AK) (3809) TTCACTAATGCCTGGTGCTGGCTAGATTTCTTGATCGTTGATGTTTCT
JeongAF225987    (4273) TTCACTAATGCCTGGTGCTGGCTAGATTTCTTGATCGTTGATGTTTCT
Consensus (4273) TTCACTAATGCCTGGTGCTGGCTAGATTTCTTGATCGTTGATGTTTCT
                                                                              Section 91
                (4321) 4321        4330        4340        4350              4368
ClareAJ251507 (4014) TTGGTTAGCCTGGTAGCCAATGCTCTTGGCTACTCAGAACTCGGTGCC
huNaIII18 (AK) (3857) TTGGTTAGCCTGGTAGCCAATGCTCTTGGCTACTCAGAACTCGGTGCC
JeongAF225987    (4321) TTGGTTAGCCTGGTAGCCAATGCTCTTGGCTACTCAGAACTCGGTGCC
Consensus (4321) TTGGTTAGCCTGGTAGCCAATGCTCTTGGCTACTCAGAACTCGGTGCC
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                                                                    —— Section 92
                (4369) 4369            4380          4390          4400          4416
ClareAJ251507 (4062) ATCAAATCATTACGGACATTAAGAGCTTTAAGACCTCTAAGAGCCTTA
   huNalll18 (AK) (3905) ATCAAATCATTACGGACATTAAGAGCTTTAAGACCTCTAAGAGCCTTA
JeongAF225987    (4369) ATCAAATCATTACGGACATTAAGAGCTTTAAGACCTCTAAGAGCCTTA
   Consensus (4369) ATCAAATCATTACGGACATTAAGAGCTTTAAGACCTCTAAGAGCCTTA
                                                                    —— Section 93
                (4417) 4417            4430          4440          4450          4464
ClareAJ251507 (4110) TCCCGGTTTGAAGGCATGAGGGTGGTTGTGAATGCTCTTGTTGGAGCA
   huNalll18 (AK) (3953) TCCCGGTTTGAAGGCATGAGGGTGGTTGTGAATGCTCTTGTTGGAGCA
JeongAF225987    (4417) TCCCGGTTTGAAGGCATGAGGGTGGTTGTGAATGCTCTTGTTGGAGCA
   Consensus (4417) TCCCGGTTTGAAGGCATGAGGGTGGTTGTGAATGCTCTTGTTGGAGCA
                                                                    —— Section 94
                (4465) 4465   4470          4480          4490          4500          4512
ClareAJ251507 (4158) ATTCCCTCTATCATGAATGTGCTGTTGGTCTGTCTCATCTTCTGGTTG
   huNalll18 (AK) (4001) ATTCCCTCTATCATGAATGTGCTGTTGGTCTGTCTCATCTTCTGGTTG
JeongAF225987    (4465) ATTCCCTCTATCATGAATGTGCTGTTGGTCTGTCTCATCTTCTGGTTG
   Consensus (4465) ATTCCCTCTATCATGAATGTGCTGTTGGTCTGTCTCATCTTCTGGTTG
                                                                    —— Section 95
                (4513) 4513   4520          4530          4540          4550          4560
ClareAJ251507 (4206) ATCTTTAGCATCATGGGTGTGAATTTGTTTGCTGGCAAGTTCTACCAC
   huNalll18 (AK) (4049) ATCTTTAGCATCATGGGTGTGAATTTGTTTGCTGGCAAGTTCTACCAC
JeongAF225987    (4513) ATCTTTAGCATCATGGGTGTGAATTTGTTTGCTGGCAAGTTCTACCAC
   Consensus (4513) ATCTTTAGCATCATGGGTGTGAATTTGTTTGCTGGCAAGTTCTACCAC
                                                                    —— Section 96
                (4561) 4561   4570          4580          4590          4608
ClareAJ251507 (4254) TGTGTTAACATGACAACGGGTAACATGTTTGACATTAGTGATGTTAAC
   huNalll18 (AK) (4097) TGTGTTAACATGACAACGGGTAACATGTTTGACATTAGTGATGTTAAC
JeongAF225987    (4561) TGTGTTAACATGACAACGGGTAACATGTTTGACATTAGTGATGTTAAC
   Consensus (4561) TGTGTTAACATGACAACGGGTAACATGTTTGACATTAGTGATGTTAAC
                                                                    —— Section 97
                (4609) 4609            4620          4630          4640          4656
ClareAJ251507 (4302) AATTTGAGTGACTGTCAGGCTCTTGGCAAGCAAGCTCGGTGGAAAAAC
   huNalll18 (AK) (4145) AATTTGAGTGACTGTCAGGCTCTTGGCAAGCAAGCTCGGTGGAAAAAC
JeongAF225987    (4609) AATTTGAGTGACTGTCAGGCTCTTGGCAAGCAAGCTCGGTGGAAAAAC
   Consensus (4609) AATTTGAGTGACTGTCAGGCTCTTGGCAAGCAAGCTCGGTGGAAAAAC
                                                                    —— Section 98
                (4657) 4657            4670          4680          4690          4704
ClareAJ251507 (4350) GTGAAAGTAAACTTTGATAATGTTGGCGCTGGCTATCTTGCACTGCTT
   huNalll18 (AK) (4193) GTGAAAGTAAACTTTGATAATGTTGGCGCTGGCTATCTTGCACTGCTT
JeongAF225987    (4657) GTGAAAGTAAACTTTGATAATGTTGGCGCTGGCTATCTTGCACTGCTT
   Consensus (4657) GTGAAAGTAAACTTTGATAATGTTGGCGCTGGCTATCTTGCACTGCTT
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Section 99

| | (4705) | 4705 | 4710 | 4720 | 4730 | 4740 | 4752 |

ClareAJ251507 (4398) CAAGTGGCCACATTTAAAGGCTGGATGGATATTATGTATGCAGCTGTT
huNaIII18 (AK) (4241) CAAGTGGCCACATTTAAAGGCTGGATGGATATTATGTATGCAGCTGTT
JeongAF225987 (4705) CAAGTGGCCACATTTAAAGGCTGGATGGATATTATGTATGCAGCTGTT
Consensus (4705) CAAGTGGCCACATTTAAAGGCTGGATGGATATTATGTATGCAGCTGTT

Section 100

| | (4753) | 4753 | 4760 | 4770 | 4780 | 4790 | 4800 |

ClareAJ251507 (4446) GATTCACGAGATGTTAAACTTCAGCCTGTATATGAAGAAAATCTGTAC
huNaIII18 (AK) (4289) GATTCACGAGATGTTAAACTTCAGCCTGTATATGAAGAAAATCTGTAC
JeongAF225987 (4753) GATTCACGAGATGTTAAACTTCAGCCTGTATATGAAGAAAATCTGTAC
Consensus (4753) GATTCACGAGATGTTAAACTTCAGCCTGTATATGAAGAAAATCTGTAC

Section 101

| | (4801) | 4801 | 4810 | 4820 | 4830 | 4848 |

ClareAJ251507 (4494) ATGTATTTATACTTTGTCATCTTTATCATCTTTGGGTCATTCTTCACT
huNaIII18 (AK) (4337) ATGTATTTATACTTTGTCATCTTTATCATCTTTGGGTCATTCTTCACT
JeongAF225987 (4801) ATGTATTTATACTTTGTCATCTTTATCATCTTTGGGTCATTCTTCACT
Consensus (4801) ATGTATTTATACTTTGTCATCTTTATCATCTTTGGGTCATTCTTCACT

Section 102

| | (4849) | 4849 | 4860 | 4870 | 4880 | 4896 |

ClareAJ251507 (4542) CTGAATCTATTCATTGGTGTCATCATAGATAACTTCAACCAGCAGAAA
huNaIII18 (AK) (4385) CTGAATCTATTCATTGGTGTCATCATAGATAACTTCAACCAGCAGAAA
JeongAF225987 (4849) CTGAATCTATTCATTGGTGTCATCATAGATAACTTCAACCAGCAGAAA
Consensus (4849) CTGAATCTATTCATTGGTGTCATCATAGATAACTTCAACCAGCAGAAA

Section 103

| | (4897) | 4897 | 4910 | 4920 | 4930 | 4944 |

ClareAJ251507 (4590) AAGAAGTTTGGAGGTCAAGACATCTTTATGACAGAGGAACAGAAAAAA
huNaIII18 (AK) (4433) AAGAAGTTTGGAGGTCAAGACATCTTTATGACAGAGGAACAGAAAAAA
JeongAF225987 (4897) AAGAAGTTTGGAGGTCAAGACATCTTTATGACAGAGGAACAGAAAAAA
Consensus (4897) AAGAAGTTTGGAGGTCAAGACATCTTTATGACAGAGGAACAGAAAAAA

Section 104

| | (4945) | 4945 | 4950 | 4960 | 4970 | 4980 | 4992 |

ClareAJ251507 (4638) TATTACAATGCAATGAAGAAACTTGGATCCAAGAAACCTCAGAAACCC
huNaIII18 (AK) (4481) TATTACAATGCAATGAAGAAACTTGGATCCAAGAAACCTCAGAAACCC
JeongAF225987 (4945) TATTACAATGCAATGAAGAAACTTGGATCCAAGAAACCTCAGAAACCC
Consensus (4945) TATTACAATGCAATGAAGAAACTTGGATCCAAGAAACCTCAGAAACCC

Section 105

| | (4993) | 4993 | 5000 | 5010 | 5020 | 5030 | 5040 |

ClareAJ251507 (4686) ATACCTCGCCCAGCAAACAAATTCCAAGGAATGGTCTTTGATTTTGTA
huNaIII18 (AK) (4529) ATACCTCGCCCAGCAAACAAATTCCAAGGAATGGTCTTTGATTTTGTA
JeongAF225987 (4993) ATACCTCGCCCAGCAAACAAATTCCAAGGAATGGTCTTTGATTTTGTA
Consensus (4993) ATACCTCGCCCAGCAAACAAATTCCAAGGAATGGTCTTTGATTTTGTA

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                                                                      ─── Section 106
              (5041) 5041        5050       5060        5070              5088
ClareAJ251507 (4734) ACCAGACAAGTCTTTGATATCAGCATCATGATCCTCATCTGCCTCAAC
   huNalll18 (AK) (4577) ACCAGACAAGTCTTTGATATCAGCATCATGATCCTCATCTGCCTCAAC
JeongAF225987   (5041) ACCAGACAAGTCTTTGATATCAGCATCATGATCCTCATCTGCCTCAAC
  Consensus (5041) ACCAGACAAGTCTTTGATATCAGCATCATGATCCTCATCTGCCTCAAC
                                                                      ─── Section 107
              (5089) 5089        5100       5110        5120              5136
ClareAJ251507 (4782) ATGGTCACCATGATGGTGGAAACGGATGACCAGGGCAAATACATGACC
   huNalll18 (AK) (4625) ATGGTCACCATGATGGTGGAAACGGATGACCAGGGCAAATACATGACC
JeongAF225987   (5089) ATGGTCACCATGATGGTGGAAACGGATGACCAGGGCAAATACATGACC
  Consensus (5089) ATGGTCACCATGATGGTGGAAACGGATGACCAGGGCAAATACATGACC
                                                                      ─── Section 108
              (5137) 5137        5150       5160        5170              5184
ClareAJ251507 (4830) CTAGTTTTGTCCCGGATCAACCTAGTGTTCATTGTTCTGTTCACTGGA
   huNalll18 (AK) (4673) CTAGTTTTGTCCCGGATCAACCTAGTGTTCATTGTTCTGTTCACTGGA
JeongAF225987   (5137) CTAGTTTTGTCCCGGATCAACCTAGTGTTCATTGTTCTGTTCACTGGA
  Consensus (5137) CTAGTTTTGTCCCGGATCAACCTAGTGTTCATTGTTCTGTTCACTGGA
                                                                      ─── Section 109
              (5185) 5185  5190       5200        5210        5220        5232
ClareAJ251507 (4878) GAATTTGTGCTGA GCTCGT TCCCTCAGACACTACTACTTCACTATA
   huNalll18 (AK) (4721) GAATTTGTGCTGAGGCTCGT TCCCTCAGACACTACTACTTCACTATA
JeongAF225987   (5185) GAATTTGTGCTGA GCTCGTTTCCCTCAGACACTACTACTTCACTATA
  Consensus (5185) GAATTTGTGCTGAAGCTCGTCTCCCTCAGACACTACTACTTCACTATA
                                                                      ─── Section 110
              (5233) 5233   5240       5250        5260        5270       5280
ClareAJ251507 (4926) GGCTGGAACATCTTTGACTTTGTGGTGGTGATTCTCTCCATTGTAGGT
   huNalll18 (AK) (4769) GGCTGGAACATCTTTGACTTTGTGGTGGTGATTCTCTCCATTGTAGGT
JeongAF225987   (5233) GGCTGGAACATCTTTGACTTTGTGGTGGTGATTCTCTCCATTGTAGGT
  Consensus (5233) GGCTGGAACATCTTTGACTTTGTGGTGGTGATTCTCTCCATTGTAGGT
                                                                      ─── Section 111
              (5281) 5281   5290       5300        5310              5328
ClareAJ251507 (4974) ATGTTTCTGGCTGAGATGATAGAAAGTATT TGTGTCCCCTACCTTG
   huNalll18 (AK) (4817) ATGTTTCTGGCTGAGATGATAGAAAGTATT TGTGTCCCCTACCTTG
JeongAF225987   (5281) ATGTTTCTGGCTGAGATGATAGAAAGTATTCTGTGTCCCCTACCTTG
  Consensus (5281) ATGTTTCTGGCTGAGATGATAGAAAGTATTTTGTGTCCCCTACCTTG
                                                                      ─── Section 112
              (5329) 5329        5340        5350        5360           5376
ClareAJ251507 (5022) TTCCGAGTGATCCGTCTTGCCAGGATTGGCCGAATCCTACGTCTGATC
   huNalll18 (AK) (4865) TTCCGAGTGATCCGTCTTGCCAGGATTGGCCGAATCCTACGTCTGATC
JeongAF225987   (5329) TTCCGAGTGATCCGTCTTGCCAGGATTGGCCGAATCCTACGTCTGATC
  Consensus (5329) TTCCGAGTGATCCGTCTTGCCAGGATTGGCCGAATCCTACGTCTGATC
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                                                                    ──── Section 113
               (5377) 5377              5390        5400        5410              5424
ClareAJ251507 (5070) AAAGGAGCAAAGGGGATCCGCACGCTGCTCTTTGCTTTGATGATGTCC
  huNalll18 (AK) (4913) AAAGGAGCAAAGGGGATCCGCACGCTGCTCTTTGCTTTGATGATGTCC
JeongAF225987   (5377) AAAGGAGCAAAGGGGATCCGCACGCTGCTCTTTGCTTTGATGATGTCC
    Consensus (5377) AAAGGAGCAAAGGGGATCCGCACGCTGCTCTTTGCTTTGATGATGTCC
                                                                    ──── Section 114
               (5425) 5425  5430       5440        5450        5460              5472
ClareAJ251507 (5118) CTTCCTGCGTTGTTTAACATCGGCCTCCTGCTCTTCCTGGTCATGTTT
  huNalll18 (AK) (4961) CTTCCTGCGTTGTTTAACATCGGCCTCCTGCTCTTCCTGGTCATGTTT
JeongAF225987   (5425) CTTCCTGCGTTGTTTAACATCGGCCTCCTGCTCTTCCTGGTCATGTTT
    Consensus (5425) CTTCCTGCGTTGTTTAACATCGGCCTCCTGCTCTTCCTGGTCATGTTT
                                                                    ──── Section 115
               (5473) 5473     5480       5490        5500        5510          5520
ClareAJ251507 (5166) ATCTATGCCATCTTTGGGATGTCCAACTTTGCCTATGTTAAAAAGGAA
  huNalll18 (AK) (5009) ATCTATGCCATCTTTGGGATGTCCAACTTTGCCTATGTTAAAAAGGAA
JeongAF225987   (5473) ATCTATGCCATCTTTGGGATGTCCAACTTTGCCTATGTTAAAAAGGAA
    Consensus (5473) ATCTATGCCATCTTTGGGATGTCCAACTTTGCCTATGTTAAAAAGGAA
                                                                    ──── Section 116
               (5521) 5521        5530        5540        5550              5568
ClareAJ251507 (5214) GCTGGAATTGATGACATGTTCAACTTTGAGACCTTTGGCAACAGCATG
  huNalll18 (AK) (5057) GCTGGAATTGATGACATGTTCAACTTTGAGACCTTTGGCAACAGCATG
JeongAF225987   (5521) GCTGGAATTGATGACATGTTCAACTTTGAGACCTTTGGCAACAGCATG
    Consensus (5521) GCTGGAATTGATGACATGTTCAACTTTGAGACCTTTGGCAACAGCATG
                                                                    ──── Section 117
               (5569) 5569        5580        5590        5600              5616
ClareAJ251507 (5262) ATCTGCTTGTTCCAAATTACAACCTCTGCTGGCTGGGATGGATTGCTA
  huNalll18 (AK) (5105) ATCTGCTTGTTCCAAATTACAACCTCTGCTGGCTGGGATGGATTGCTA
JeongAF225987   (5569) ATCTGCTTGTTCCAAATTACAACCTCTGCTGGCTGGGATGGATTGCTA
    Consensus (5569) ATCTGCTTGTTCCAAATTACAACCTCTGCTGGCTGGGATGGATTGCTA
                                                                    ──── Section 118
               (5617) 5617          5630        5640        5650              5664
ClareAJ251507 (5310) GCACCTATTCTTAATAGTGCACCACCCGACTGTGACCCTGACACAATT
  huNalll18 (AK) (5153) GCACCTATTCTTAATAGTGCACCACCCGACTGTGACCCTGACACAATT
JeongAF225987   (5617) GCACCTATTCTTAATAGTGCACCACCCGACTGTGACCCTGACACAATT
    Consensus (5617) GCACCTATTCTTAATAGTGCACCACCCGACTGTGACCCTGACACAATT
                                                                    ──── Section 119
               (5665) 5665  5670       5680        5690        5700              5712
ClareAJ251507 (5358) CACCCTGGCAGCTCAGTTAAGGGAGACTGTGGGAACCCATCTGTTGGG
  huNalll18 (AK) (5201) CACCCTGGCAGCTCAGTTAAGGGAGACTGTGGGAACCCATCTGTTGGG
JeongAF225987   (5665) CACCCTGGCAGCTCAGTTAAGGGAGACCGTGGGGACCCATCTGTTGGG
    Consensus (5665) CACCCTGGCAGCTCAGTTAAGGGAGACTGTGGGAACCCATCTGTTGGG
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─── Section 120

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              (5713) 5713      5720       5730        5740        5750       5760
ClareAJ251507 (5406) ATTTTCTTTTTCGTCAGTTACATCATCATATCCTTCCTGGTTGTGGTG
huNaIII18 (AK) (5249) ATTTTCTTTTTTGTCAGTTACATCATCATATCCTTCCTGGTTGTGGTG
JeongAF225987  (5713) ATTTTCTTTTTTGTCAGTTACATCATCATATCCTTCCTGGTTGTGGTG
   Consensus (5713) ATTTTCTTTTTTGTCAGTTACATCATCATATCCTTCCTGGTTGTGGTG
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─── Section 121

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              (5761) 5761     5770        5780       5790            5808
ClareAJ251507 (5454) AACATGTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCTACTGAA
huNaIII18 (AK) (5297) AACATGTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCTACTGAA
JeongAF225987  (5761) AACATGTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCTACTGAA
   Consensus (5761) AACATGTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCTACTGAA
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─── Section 122

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              (5809) 5809      5820       5830        5840            5856
ClareAJ251507 (5502) GAAAGTGCAGAGCCCCTGAGTGAGGATGACTTTGAGATGTTCTATGAG
huNaIII18 (AK) (5345) GAAAGTGCAGAGCCCCTGAGTGAGGATGACTTTGAGATGTTCTATGAG
JeongAF225987  (5809) GAAAGTGCAGAGCCCCTGAGTGAGGATGACTTTGAGATGTTCTATGAG
   Consensus (5809) GAAAGTGCAGAGCCCCTGAGTGAGGATGACTTTGAGATGTTCTATGAG
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─── Section 123

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              (5857) 5857       5870        5880        5890           5904
ClareAJ251507 (5550) GTTTGGGAAAAGTTTGATCCCGATGCGACCCAGTTTATAGAGTTCTCT
huNaIII18 (AK) (5393) GTTTGGGAAAAGTTTGATCCCGATGCGACCCAGTTTATAGAGTTCTCT
JeongAF225987  (5857) GTTTGGGAAAAGTTTGATCCCGATGCGACCCAGTTTATAGAGTTCTCT
   Consensus (5857) GTTTGGGAAAAGTTTGATCCCGATGCGACCCAGTTTATAGAGTTCTCT
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─── Section 124

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              (5905) 5905    5910        5920        5930        5940       5952
ClareAJ251507 (5598) AAACTCTCTGATTTTGCAGCTGCCCTGGATCCTCCTCTTCTCATAGCA
huNaIII18 (AK) (5441) AAACTCTCTGATTTTGCAGCTGCCCTGGATCCTCCTCTTCTCATAGCA
JeongAF225987  (5905) AAACTCTCTGATTTTGCAGCTGCCCTGGATCCTCCTCTTCTCATAGCA
   Consensus (5905) AAACTCTCTGATTTTGCAGCTGCCCTGGATCCTCCTCTTCTCATAGCA
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─── Section 125

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              (5953) 5953     5960      5970        5980        5990       6000
ClareAJ251507 (5646) AAACCCAACAAAGTCCAGCTTATTGCCATGGATCTGCCCATGGTCAGT
huNaIII18 (AK) (5489) AAACCCAACAAAGTCCAGCTTATTGCCATGGATCTGCCCATGGTCAGT
JeongAF225987  (5953) AAACCCAACAAAGTCCAGCTTATTGCCATGGATCTGCCCATGGTCAGT
   Consensus (5953) AAACCCAACAAAGTCCAGCTTATTGCCATGGATCTGCCCATGGTCAGT
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─── Section 126

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              (6001) 6001      6010       6020        6030           6048
ClareAJ251507 (5694) GGTGACCGGATCCACTGTCTTGATATTTTATTTGCCTTTACAAAGCGT
huNaIII18 (AK) (5537) GGTGACCGGATCCACTGTCTTGATATTTTATTTGCCTTTACAAAGCGT
JeongAF225987  (6001) GGTGACCGGATCCACTGTCTTGATATTTTATTTGCCTTTACAAAGCGT
   Consensus (6001) GGTGACCGGATCCACTGTCTTGATATTTTATTTGCCTTTACAAAGCGT
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                                                                    Section 127
            (6049) 6049          6060          6070          6080          6096
ClareAJ251507 (5742) GTTTTGGGTGAGAGTGGAGAGATGGATGCCCTTCGAATACAGATGGAA
   huNalll18 (AK) (5585) GTTTTGGGTGAGAGTGGAGAGATGGATGCCCTTCGAATACAGATGGAA
JeongAF225987    (6049) GTTTTGTGTGAGAGTGGAGAGATGGATGCCCTTCGAATACAGATGGAA
     Consensus (6049) GTTTTGGGTGAGAGTGGAGAGATGGATGCCCTTCGAATACAGATGGAA
                                                                    Section 128
            (6097) 6097          6110          6120          6130          6144
ClareAJ251507 (5790) GACAGGTTTATGGCATCAAACCCCTCCAAAGTCTCTTATGAGCCTATT
   huNalll18 (AK) (5633) GACAGGTTTATGGCATCAAACCCCTCCAAAGTCTCTTATGAGCCTATT
JeongAF225987    (6097) GACAGGTTTATGGCATCAAACCCCTCCAAAGTCTCTTATGAGCCTATT
     Consensus (6097) GACAGGTTTATGGCATCAAACCCCTCCAAAGTCTCTTATGAGCCTATT
                                                                    Section 129
            (6145) 6145  6150          6160          6170          6180          6192
ClareAJ251507 (5838) ACAACCACTTTGAAACGTAAACAAGAGGAGGTGTCTGCCGCTATCATT
   huNalll18 (AK) (5681) ACAACCACTTTGAAACGTAAACAAGAGGAGGTGTCTGCCGCTATCATT
JeongAF225987    (6145) ACAACCACTTTGAAACGTAAACAAGAGGAGGTGTCTGCCGCTATCATT
     Consensus (6145) ACAACCACTTTGAAACGTAAACAAGAGGAGGTGTCTGCCGCTATCATT
                                                                    Section 130
            (6193) 6193  6200          6210          6220          6230          6240
ClareAJ251507 (5886) CAGCGTAATTTCAGATGTTATCTTTTAAAGCAAAGGTTAAAAAATATA
   huNalll18 (AK) (5729) CAGCGTAATTTCAGATGTTATCTTTTAAAGCAAAGGTTAAAAAATATA
JeongAF225987    (6193) CAGCGTAATTTCAGATGTTATCTTTTAAAGCAAAGGTTAAAAAATATA
     Consensus (6193) CAGCGTAATTTCAGATGTTATCTTTTAAAGCAAAGGTTAAAAAATATA
                                                                    Section 131
            (6241) 6241  6250          6260          6270          6288
ClareAJ251507 (5934) TCAAGTAACTATAACAAAGAGGCAATTAAAGGGAGGATTGACTTACCT
   huNalll18 (AK) (5777) TCAAGTAACTATAACAAAGAGGCAATTAAAGGGAGGATTGACTTACCT
JeongAF225987    (6241) TCAAGTAACTATAACAAAGAGGCAATTAAAGGGAGGATTGACTTACCT
     Consensus (6241) TCAAGTAACTATAACAAAGAGGCAATTAAAGGGAGGATTGACTTACCT
                                                                    Section 132
            (6289) 6289          6300          6310          6320          6336
ClareAJ251507 (5982) ATAAACAAGACATGATTATTGACAAACTAAATGGGAACTCCACTCCA
   huNalll18 (AK) (5825) ATAAACAAGACATGATTATTGACAAACTAAATGGGAACTCCACTCCA
JeongAF225987    (6289) ATAAACAAGACATGATTATTGACAAACTAAATGGGAACTCCACTCCA
     Consensus (6289) ATAAACAAGACATGATTATTGACAAACTAAATGGGAACTCCACTCCA
                                                                    Section 133
            (6337) 6337          6350          6360          6370          6384
ClareAJ251507 (6030) GAAAAAACAGATGGGAGTTCCTCTACCACCCCTCCTCCTTCCTATGAT
   huNalll18 (AK) (5873) GAAAAAACAGATGGGAGTTCCTCTACCACCCCTCCTCCTTCCTATGAT
JeongAF225987    (6337) GAAAAAACAGATGGGAGTTCCTCTACCACCCCTCCTCCTTCCTATGAT
     Consensus (6337) GAAAAAACAGATGGGAGTTCCTCTACCACCTCTCCTCCTTCCTATGAT
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                                                                    Section 134
                   (6385) 6385    6390        6400        6410        6420        6432
       ClareAJ251507 (6078) AGTGTAACAAAACCAGACAAGGAAAAGTTTGAGAAAGACAAACCAGAA
        huNalll18 (AK) (5921) AGTGTAACAAAACCAGACAAGGAAAAGTTTGAGAAAGACAAACCAGAA
     JeongAF225987     (6385) AGTGTAACAAAACCAGACAAGGAAAAGTTTGAGAAAGACAAACCAGAA
         Consensus (6385) AGTGTAACAAAACCAGACAAGGAAAAGTTTGAGAAAGACAAACCAGAA
                                                                    Section 135
                   (6433) 6433    6440        6450        6460        6470        6480
       ClareAJ251507 (6126) AAAGAAAGCAAAGGAAAAGAGGTCAGAGAAAATCAAAAGTAAAAAGAA
        huNalll18 (AK) (5969) AAAGAAAGCAAAGGAAAAGAGGTCAGAGAAAATCAAAAGTAAAAAGAA
     JeongAF225987     (6433) AAAGAAAGCAAAGGAAAAGAGGTCAGAGAAAATCAAAAGTAAAAAGAA
         Consensus (6433) AAAGAAAGCAAAGGAAAAGAGGTCAGAGAAAATCAAAAGTAAAAAGAA
                                                                    Section 136
                   (6481) 6481    6490        6500        6510        6528
       ClareAJ251507 (6174) ACAAAGAATTATCTTTGTGATCAATTGTTTACAGCCTATGAAGGTAAA
        huNalll18 (AK) (6017) ACAAAGAATTATCTTTGTGATCAATTGTTTACAGCCTATGAAGGTAAA
     JeongAF225987     (6481) ACAAAGAATTATCTTTGTGATCAATTGTTTACAGCCTATGAAGGTAAA
         Consensus (6481) ACAAAGAATTATCTTTGTGATCAATTGTTTACAGCCTATGAAGGTAAA
                                                                    Section 137
                   (6529) 6529    6540        6550        6560        6576
       ClareAJ251507 (6222) GTATATGTGTCAACTGGACTTCAAGAGGAGGTCCATGCCAAACTGACT
        huNalll18 (AK) (6065) GTATATGTGTCAACTGGACTTCAAG------------------------
     JeongAF225987     (6529) GTATATGTGTCAACTGGACTTCAAGAGGAGGTCCATGCCAAACTGACT
         Consensus (6529) GTATATGTGTCAACTGGACTTCAAGAGGAGGTCCATGCCAAACTGACT
                                                                    Section 138
                   (6577) 6577         6590        6600        6610        6624
       ClareAJ251507 (6270) GTTTTAACAAATACTCATAGTCAGTGCCTATACAAGACAGTGAAGTGA
        huNalll18 (AK) (6090) ------------------------------------------------
     JeongAF225987     (6577) GTTTTAACAAATACTCATAGTCAGTGCCTATACAAGACAGTGAAGTGA
         Consensus (6577) GTTTTAACAAATACTCATAGTCAGTGCCTATACAAGACAGTGAAGTGA
                                                                    Section 139
                   (6625) 6625  6630        6640        6650        6660        6672
       ClareAJ251507 (6318) CCTCTCTGTCACTGCAACTCTGTGAAGCAGGGTATCAAC A TTGACAAG
        huNalll18 (AK) (6090) ------------------------------------------------
     JeongAF225987     (6625) CCTCTCTGTCACTGCAACTCTGTGAAGCAGGGTATCAAC G TTGACAAG
         Consensus (6625) CCTCTCTGTCACTGCAACTCTGTGAAGCAGGGTATCAAC  TTGACAAG
                                                                    Section 140
                   (6673) 6673    6680        6690        6700        6710        6720
       ClareAJ251507 (6366) AGGTTGCTGTTTTTATTACCAGCTGACACTGCTGAGGAGAAACCCAAT
        huNalll18 (AK) (6090) ------------------------------------------------
     JeongAF225987     (6673) AGGTTGCTGTTTTTATTACCAGCTGACACTGCTGAGGAGAAACCCAAT
         Consensus (6673) AGGTTGCTGTTTTTATTACCAGCTGACACTGCTGAGGAGAAACCCAAT
```

—— Section 141

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           (6721) 6721        6730        6740        6750              6768
ClareAJ251507 (6414) GGCTACCTAGACTATAGGGATAGTTGTGCAAAGTGAACATTGTAACTA
   huNalll18 (AK) (6090) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987   (6721) GGCTACCTAGACTATAGGGATAGTTGTGCAAAGTGAACATTGTAACTA
   Consensus (6721) GGCTACCTAGACTATAGGGATAGTTGTGCAAAGTGAACATTGTAACTA
```

—— Section 142

```
           (6769) 6769        6780        6790        6800         6816
ClareAJ251507 (6462) CACCAAACACCTTTAGTACAGTCCTTGCATCCATTCTATTTTTAACTT
   huNalll18 (AK) (6090) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987   (6769) CACCAAACACCTTTAGTACAGTCCTTGCATCCATTCTATTTTTAACTT
   Consensus (6769) CACCAAACACCTTTAGTACAGTCCTTGCATCCATTCTATTTTTAACTT
```

—— Section 143

```
           (6817) 6817        6830        6840        6850         6864
ClareAJ251507 (6510) CCATATCTGCCATATTTTTACAAAATTTGTTCTAGTGCATTTCCATGG
   huNalll18 (AK) (6090) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987   (6817) CCATATCTGCCATATTTTTACAAAATTTGTTCTAGTGCATTTCCATGG
   Consensus (6817) CCATATCTGCCATATTTTTACAAAATTTGTTCTAGTGCATTTCCATGG
```

—— Section 144

```
           (6865) 6865  6870        6880        6890        6900      6912
ClareAJ251507 (6558) TCCCCAATTCATAGTTTATTCATAATGCTATGTCACTATTTT- - - - - -
   huNalll18 (AK) (6090) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987   (6865) TCCCCAATTCATAGTTTATTCATAATGCTATGTCACTATTTTTGTAAA
   Consensus (6865) TCCCCAATTCATAGTTTATTCATAATGCTATGTCACTATTTT
```

—— Section 145

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           (6913) 6913   6920       6930        6940        6950      6960
ClareAJ251507 (6600) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
   huNalll18 (AK) (6090) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987   (6913) TGAGGTTTACGTTGAAGAAACAGTATACAAGAACCCTGTCTCTCAAAT
   Consensus (6913)
```

—— Section 146

```
           (6961) 6961   6970       6980        6990              7008
ClareAJ251507 (6600) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
   huNalll18 (AK) (6090) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987   (6961) GATCAGACAAAGGTGTTTGCCAGAGAGATAAAATTTTTGCTCAAAAC
   Consensus (6961)
```

—— Section 147

```
           (7009) 7009        7020        7030        7040         7056
ClareAJ251507 (6600) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
   huNalll18 (AK) (6090) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987   (7009) CAGAAAAGAATTGTAATGGCTACAGTTTCAGTTACTTCCATTTTCTA
   Consensus (7009)
```

—— Section 148

| (7057) | 7057 | 7070 | 7080 | 7090 | 7104 |

ClareAJ251507 (6600) —

huNaIII18 (AK) (6090) —

JeongAF225987   (7057) GATGGCTTTAATTTTGAAAGTATTTTAGTCTGTTATGTTTGTTTCTAT

Consensus (7057)

—— Section 149

| (7105) | 7105 | 7110 | 7120 | 7130 | 7140 | 7152 |

ClareAJ251507 (6600) —

huNaIII18 (AK) (6090) —

JeongAF225987   (7105) CTGAACAGTTATGTGCCTGTAAAGTCTCCTCTAATATTTAAAGGATTA

Consensus (7105)

—— Section 150

| (7153) | 7153 | 7160 | 7170 | 7180 | 7190 | 7200 |

ClareAJ251507 (6600) —

huNaIII18 (AK) (6090) —

JeongAF225987   (7153) TTTTTATGCAAAGTATTCTGTTTCAGCAAGTGCAAATTTTATTCTAAG

Consensus (7153)

—— Section 151

| (7201) | 7201 | 7210 | 7220 | 7230 | 7248 |

ClareAJ251507 (6600) —

huNaIII18 (AK) (6090) —

JeongAF225987   (7201) TTTCAGAGCTCTATATTTAATTTAGGTCAAATGCTTTCCAAAAAGTAA

Consensus (7201)

—— Section 152

| (7249) | 7249 | 7260 | 7270 | 7280 | 7296 |

ClareAJ251507 (6600) —

huNaIII18 (AK) (6090) —

JeongAF225987   (7249) TCTAATAAATCCATTCTAGAAAAATATATCTAAAGTATTGCTTTAGAA

Consensus (7249)

—— Section 153

| (7297) | 7297 | 7310 | 7320 | 7330 | 7344 |

ClareAJ251507 (6600) —

huNaIII18 (AK) (6090) —

JeongAF225987   (7297) TAGTTGTTCCACTTTCTGCTGCAGTATTGCTTTGCCATCTTCTGCTCT

Consensus (7297)

—— Section 154

| (7345) | 7345 | 7350 | 7360 | 7370 | 7380 | 7392 |

ClareAJ251507 (6600) —

huNaIII18 (AK) (6090) —

JeongAF225987   (7345) CAGCAAAGCTGATAGTCTATGTCAATTAAATACCCTATGTTATGTAAA

Consensus (7345)

Section 155
| | (7393) | 7393 | 7400 | 7410 | 7420 | 7430 | 7440 |

ClareAJ251507 (6600)   --
huNaIII18 (AK) (6090) --
JeongAF225987   (7393) TAGTTATTTTATCCTGTGGTGCATGTTTGGGCAAATATATATATAGCC
Consensus (7393)

Section 156
| | (7441) | 7441 | 7450 | 7460 | 7470 | 7488 |

ClareAJ251507 (6600)   --
huNaIII18 (AK) (6090) --
JeongAF225987   (7441) TGATAAACAACTTCTATTAAATCAAATATGTACCACAGTGTATGTGTC
Consensus (7441)

Section 157
| | (7489) | 7489 | 7500 | 7510 | 7520 | 7536 |

ClareAJ251507 (6600)   --
huNaIII18 (AK) (6090) --
JeongAF225987   (7489) TTTTGCAAGCTTCCAACAGGGATGTATCCTGTATCATTCATTAAACAT
Consensus (7489)

Section 158
| | (7537) | 7537 | 7550 | 7560 | 7570 | 7584 |

ClareAJ251507 (6600)   --
huNaIII18 (AK) (6090) --
JeongAF225987   (7537) AGTTTAAAGGCTATCACTAATGCATGTTAATATTGCCTATGCTGCTCT
Consensus (7537)

Section 159
| | (7585) | 7585 | 7590 | 7600 | 7610 | 7620 | 7632 |

ClareAJ251507 (6600)   --
huNaIII18 (AK) (6090) --
JeongAF225987   (7585) ATTTTACTCAATCCATTCTTCACAAGTCTTGGTTAAAGAATGTCACAT
Consensus (7585)

Section 160
| | (7633) | 7633 | 7640 | 7650 | 7660 | 7670 | 7680 |

ClareAJ251507 (6600)   --
huNaIII18 (AK) (6090) --
JeongAF225987   (7633) ATTGGTGATAGAATGAATTCAACCTGCTCTGTCCATTATGTCAAGCAG
Consensus (7633)

Section 161
| | (7681) | 7681 | 7690 | 7700 | 7710 | 7728 |

ClareAJ251507 (6600)   --
huNaIII18 (AK) (6090) --
JeongAF225987   (7681) AATAATTTGAAGCTATTTACAAACACCTTTACTTTTGCACTTTTAATT
Consensus (7681)

———————————————————————————————————— Section 162
(7729) 7729   7740   7750   7760   7776
ClareAJ251507 (6600) —
huNalll18 (AK) (6090) —
JeongAF225987   (7729) CAACATGAGTATCATATGGTATCTCTCTGGATTTCAAGGAAACACACT
Consensus (7729)

———————————————————————————————————— Section 163
(7777) 7777   7790   7800   7810   7824
ClareAJ251507 (6600) —
huNalll18 (AK) (6090) —
JeongAF225987   (7777) GGATACTGCCTACTGACAAAACCTATTCTTCATATTTTGCTAAAAATA
Consensus (7777)

———————————————————————————————————— Section 164
(7825) 7825   7830   7840   7850   7860   7872
ClareAJ251507 (6600) —
huNalll18 (AK) (6090) —
JeongAF225987   (7825) TGTCTAAAACTTGTTTAAATATAAATAATGTAAAAATATAATCAACTT
Consensus (7825)

———————————————————————————————————— Section 165
(7873) 7873   7880   7890   7900   7910   7920
ClareAJ251507 (6600) —
huNalll18 (AK) (6090) —
JeongAF225987   (7873) TATTTGTCAGCATTTTGTACATAAGAAAATTATTTTCAGGTTGATGAC
Consensus (7873)

———————————————————————————————————— Section 166
(7921) 7921   7930   7940   7950   7968
ClareAJ251507 (6600) —
huNalll18 (AK) (6090) —
JeongAF225987   (7921) ATCACAATTTATTTTACTTTATGCTTTTGCTTTTGATTTTTAATCACA
Consensus (7921)

———————————————————————————————————— Section 167
(7969) 7969   7980   7990   8000   8016
ClareAJ251507 (6600) —
huNalll18 (AK) (6090) —
JeongAF225987   (7969) ATTCCAAACTTTTGAATCCATAAGATTTTTCAATGGATAATTTCCTAA
Consensus (7969)

———————————————————————————————————— Section 168
(8017) 8017   8030   8040   8050   8064
ClareAJ251507 (6600) —
huNalll18 (AK) (6090) —
JeongAF225987   (8017) AATAAAAGTTAGATAATGGGTTTTATGGATTTCTTTGTTATAATATAT
Consensus (8017)

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───────────────────────────────────────────────────────── Section 169
        (8065)  8065    8070        8080        8090        8100        8112
ClareAJ251507 (6600)  – – – – – – – – – – – – – – – – – – – – – – – – – – – – – – –
   huNalll18 (AK) (6090)  – – – – – – – – – – – – – – – – – – – – – – – – – – – – – – –
JeongAF225987    (8065)  TTTCTACCATTCCAATAGGAGATACATTGGTCAAACACTCAAACCTAG
    Consensus (8065)

───────────────────────────────────────────────────────── Section 170
        (8113)  8113    8120        8130        8140        8150        8160
ClareAJ251507 (6600)  – – – – – – – – – – – – – – – – – – – – – – – – – – – – – – –
   huNalll18 (AK) (6090)  – – – – – – – – – – – – – – – – – – – – – – – – – – – – – – –
JeongAF225987    (8113)  ATCATTTTCTACCAACTATGGTTGCCTCAATATAACCTTTTATTCATA
    Consensus (8113)

───────────────────────────────────────────────────────── Section 171
        (8161)  8161    8170        8180        8190                    8208
ClareAJ251507 (6600)  – – – – – – – – – – – – – – – – – – – – – – – – – – – – – – –
   huNalll18 (AK) (6090)  – – – – – – – – – – – – – – – – – – – – – – – – – – – – – – –
JeongAF225987    (8161)  GATGTTTTTTTTTATTCAACTTTTGTAGTATTTACGTATGCAGACTAG
    Consensus (8161)

───────────────────────────────────────────────────────── Section 172
        (8209)  8209        8220        8230        8240            8256
ClareAJ251507 (6600)  – – – – – – – – – – – – – – – – – – – – – – – – – – – – – – –
   huNalll18 (AK) (6090)  – – – – – – – – – – – – – – – – – – – – – – – – – – – – – – –
JeongAF225987    (8209)  TCTTATTTTTTTAATTCCTGCTGCACTAAAGCTATTACAAATATAACA
    Consensus (8209)

───────────────────────────────────────────────────────── Section 173
        (8257)  8257            8270        8280        8290        8304
ClareAJ251507 (6600)  – – – – – – – – – – – – – – – – – – – – – – – – – – – – – – –
   huNalll18 (AK) (6090)  – – – – – – – – – – – – – – – – – – – – – – – – – – – – – – –
JeongAF225987    (8257)  TGGACTTTGTTCTTTTTAGCCATGAACAAAGTGGCAAAGTTGTGCAAT
    Consensus (8257)

───────────────────────────────────────────────────────── Section 174
        (8305)  8305    8310        8320        8330        8340        8352
ClareAJ251507 (6600)  – – – – – – – – – – – – – – – – – – – – – – – – – – – – – – –
   huNalll18 (AK) (6090)  – – – – – – – – – – – – – – – – – – – – – – – – – – – – – – –
JeongAF225987    (8305)  TACCTAACATGATATAAATTTTTGTTTTTTGCACAAACCAAAAGTTTA
    Consensus (8305)

───────────────────────────────────────────────────────── Section 175
        (8353)  8353    8360        8370        8380        8390        8400
ClareAJ251507 (6600)  – – – – – – – – – – – – – – – – – – – – – – – – – – – – – – –
   huNalll18 (AK) (6090)  – – – – – – – – – – – – – – – – – – – – – – – – – – – – – – –
JeongAF225987    (8353)  ATGTTAATTCTTTTTACAAACTATTTACTGTAGTGTATTGAAGAACT
    Consensus (8353)
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                                                                        Section 176
          (8401)  8401          8410          8420          8430                    8448
ClareAJ251507 (6600)  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
  huNalll18 (AK) (6090)  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987    (8401)  GCATGCAGGGAATTGCTATTGCTAAAAGAATGGTGAGCTACGTCATT
    Consensus (8401)
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                                                                        Section 177
          (8449)  8449          8460          8470          8480          8496
ClareAJ251507 (6600)  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
  huNalll18 (AK) (6090)  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987    (8449)  ATTGAGCCAAAAGAATAAATTTCATTTTTTATTGCATTTCACTTATTG
    Consensus (8449)
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                                                                        Section 178
          (8497)  8497            8510        8520        8530          8544
ClareAJ251507 (6600)  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
  huNalll18 (AK) (6090)  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987    (8497)  GGCTCTGGGGTTTTTTGTTTTTGTTTTTTGCTGTTGGCAGTTTAAAAT
    Consensus (8497)
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                                                                        Section 179
          (8545)  8545    8550          8560          8570          8580          8592
ClareAJ251507 (6600)  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
  huNalll18 (AK) (6090)  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987    (8545)  ATATATAATTAATAAAACCTGTGCTTGATCTGACATTTGTATACATAA
    Consensus (8545)
```

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                                                                        Section 180
          (8593)  8593    8600          8610          8620          8630          8640
ClareAJ251507 (6600)  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
  huNalll18 (AK) (6090)  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987    (8593)  AAGTTTACATGAATTTTACAACAAACTAGTGCATGATTCACCAAGCAG
    Consensus (8593)
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                                                                        Section 181
          (8641)  8641          8650          8660          8670                    8688
ClareAJ251507 (6600)  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
  huNalll18 (AK) (6090)  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987    (8641)  TACTACAGAACAAAGGCAAATTAAAAGCAGCTTTGTGAACTTTTATGT
    Consensus (8641)
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                                                                        Section 182
          (8689)  8689          8700          8710          8720          8736
ClareAJ251507 (6600)  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
  huNalll18 (AK) (6090)  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987    (8689)  GTGCAAAGGATCAAGTTCACATGTTCCAACTTTCAGGTTTGATAATAA
    Consensus (8689)
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─────────────────────────────────────────────────────────────── Section 183
              (8737) 8737              8750        8760        8770        8784
ClareAJ251507 (6600) ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─
huNalll18 (AK) (6090) ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─
JeongAF225987   (8737) TAGTAGTAACCACCTACAATAGCTTTCAATTTCAATTAACTCCCTTGG
Consensus (8737)

─────────────────────────────────────────────────────────────── Section 184
              (8785) 8785  8790         8800        8810        8820        8832
ClareAJ251507 (6600) ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─
huNalll18 (AK) (6090) ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─
JeongAF225987   (8785) CTATAAGCATCTAAACTCATCTTCTTTCAATATAATTGATGCTATCTC
Consensus (8785)

─────────────────────────────────────────────────────────────── Section 185
              (8833) 8833      8840        8850        8860        8870        8880
ClareAJ251507 (6600) ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─
huNalll18 (AK) (6090) ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─
JeongAF225987   (8833) CTAATTACTTGGTGGCTAATAAATGTTACATTCTTTGTTACTTAAATG
Consensus (8833)

─────────────────────────────────────────────────────────────── Section 186
              (8881) 8881      8890        8900        8910              8928
ClareAJ251507 (6600) ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─
huNalll18 (AK) (6090) ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─
JeongAF225987   (8881) CATTATATAAACTCCTATGTATACATAAGGTATTAATGATATAGTTAT
Consensus (8881)

─────────────────────────────────────────────────────────────── Section 187
              (8929) 8929         8940        8950        8960          8976
ClareAJ251507 (6600) ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─
huNalll18 (AK) (6090) ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─
JeongAF225987   (8929) TGAGAATTTATATTAACTTTTTTTTCAAGAACCCTTGGATTTATGTGA
Consensus (8929)

─────────────────────────────────────────────────────────────── Section 188
              (8977) 8977            8990        9000        9010        9024
ClareAJ251507 (6600) ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─
huNalll18 (AK) (6090) ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─
JeongAF225987   (8977) GGTCAAAACCAAACTCTTATTCTCAGTGGAAAACTCCAGTTGTAATGC
Consensus (8977)

─────────────────────────────────────────────────────────────── Section 189
              (9025) 9025  9030        9040        9050        9060        9072
ClareAJ251507 (6600) ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─
huNalll18 (AK) (6090) ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─
JeongAF225987   (9025) ATATTTTTAAAGACAATTTGGATCTAAATATGTATTTCATAATTCTCC
Consensus (9025)
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                                                            Section 190
       (9073) 9073      9080        9090       9100       9110      9120
ClareAJ251507 (6600) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
huNaIII18 (AK) (6090) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
JeongAF225987    (9073) C A T A A T A A A T T A T A T A A G G T G G A A A A A A A A A A A A A A A A A A A A A A A A A A A
Consensus (9073)
                                                            Section 191
       (9121) 9123
ClareAJ251507 (6600) - - -
huNaIII18 (AK) (6090) - - -
JeongAF225987    (9121) A A A
Consensus (9121)
```

	(1) 1 10 20 30 40
ClareAJ251507protein	(1) MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKE
Translation of huNaIII18 (AK)	(1) MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKE
Translation of JeongAF225987	(1) MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKE
Consensus	(1) MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKE

Section 2

	(41) 41 50 60 70 80
ClareAJ251507protein	(41) QDNDDENKPKPNSDLEAGKNLPFIYGDIPPEMVSEPLEDL
Translation of huNaIII18 (AK)	(41) QDNDDENKPKPNSDLEAGKNLPFIYGDIPPEMVSEPLEDL
Translation of JeongAF225987	(41) QDNDDENKPKPNSDLEAGKNLPFIYGDIPPEMVSEPLEDL
Consensus	(41) QDNDDENKPKPNSDLEAGKNLPFIYGDIPPEMVSEPLEDL

Section 3

	(81) 81 90 100 110 120
ClareAJ251507protein	(81) DPYYINKKTFIVMNKGKAIFRFSATSALYILTPLNPVRKI
Translation of huNaIII18 (AK)	(81) DPYYINKKTFIVMNKGKAIFRFSATSALYILTPLNPVRKI
Translation of JeongAF225987	(81) DPYYINKKTFIVMNKGKAIFRFSATSALYILTPLNPVRKI
Consensus	(81) DPYYINKKTFIVMNKGKAIFRFSATSALYILTPLNPVRKI

Section 4

	(121) 121 130 140 150 160
ClareAJ251507protein	(121) AIKILVHSLFSMLIMCTILTNCVFMTLSNPPDWTKNVEYT
Translation of huNaIII18 (AK)	(121) AIKILVHSLFSMLIMCTILTNCVFMTLSNPPDWTKNVEYT
Translation of JeongAF225987	(121) AIKILVHSLFSMLIMCTILTNCVFMTLSNPPDWTKNVEYT
Consensus	(121) AIKILVHSLFSMLIMCTILTNCVFMTLSNPPDWTKNVEYT

Section 5

	(161) 161 170 180 190 200
ClareAJ251507protein	(161) FTGIYTFESLIKILARGFCLEDFTFLRDPWNWLDFSVIVM
Translation of huNaIII18 (AK)	(161) FTGIYTFESLIKILARGFCLEDFTFLRDPWNWLDFSVIVM
Translation of JeongAF225987	(161) FTGIYTFESLIKILARGFCLEDFTFLRDPWNWLDFSVIVM
Consensus	(161) FTGIYTFESLIKILARGFCLEDFTFLRDPWNWLDFSVIVM

Section 6

	(201) 201 210 220 230 240
ClareAJ251507protein	(201) AYVTEFVSLGNVSALRTFRVLRALKTISVIPGLKTIVGAL
Translation of huNaIII18 (AK)	(201) AYVTEFVSLGNVSALRTFRVLRALKTISVIPGLKTIVGAL
Translation of JeongAF225987	(201) AYVTEFVDLGNVSALRTFRVLRALKTISVIPGLKTIVGAL
Consensus	(201) AYVTEFVSLGNVSALRTFRVLRALKTISVIPGLKTIVGAL

Section 7

	(241) 241 250 260 270 280
ClareAJ251507protein	(241) IQSVKKLSDVMILTVFCLSVFALIGLQLFMGNLRNKCLQW
Translation of huNaIII18 (AK)	(241) IQSVKKLSDVMILTVFCLSVFALIGLQLFMGNLRNKCLQW
Translation of JeongAF225987	(241) IQSVKKLSDVMILTVFCLSVFALIGLQLFMGNLRNKCLQW
Consensus	(241) IQSVKKLSDVMILTVFCLSVFALIGLQLFMGNLRNKCLQW

——————————————————————————————————— Section 8

		281	290	300	310	320
	(281)					
ClareAJ251507protein	(281)	PPSDSAFETNTTSYFNGTMDSNGTFVNVTMSTFNWKDYIG				
Translation of huNaIII18 (AK)	(281)	PPSDSAFETNTTSYFNGTMDSNGTFVNVTMSTFNWKDYIG				
Translation of JeongAF225987	(281)	PPSDSAFETNTTSYFNGTMDSNGTFVNVTMSTFNWKDYIG				
Consensus	(281)	PPSDSAFETNTTSYFNGTMDSNGTFVNVTMSTFNWKDYIG				

——————————————————————————————————— Section 9

		321	330	340	350	360
ClareAJ251507protein	(321)	DDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRNPN				
Translation of huNaIII18 (AK)	(321)	DDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRNPN				
Translation of JeongAF225987	(321)	DDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRNPN				
Consensus	(321)	DDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRNPN				

——————————————————————————————————— Section 10

		361	370	380	390	400
ClareAJ251507protein	(361)	YGYTSFDTFSWAFLSLFRLMTQDYWENLYQLTLRAAGKTY				
Translation of huNaIII18 (AK)	(361)	YGYTSFDTFSWAFLSLFRLMTQDYWENLYQLTLRAAGKTY				
Translation of JeongAF225987	(361)	YGYTSFDTFSWAFLSLFRLMTQDYWENLYQLTLRAAGKTY				
Consensus	(361)	YGYTSFDTFSWAFLSLFRLMTQDYWENLYQLTLRAAGKTY				

——————————————————————————————————— Section 11

		401	410	420	430	440
ClareAJ251507protein	(401)	MIFFVLVIFLGSFYLVNLILAVVAMAYEEQNQATLEEAEQ				
Translation of huNaIII18 (AK)	(401)	MIFFVLVIFLGSFYLVNLILAVVAMAYEEQNQATLEEAEQ				
Translation of JeongAF225987	(401)	MIFFVLVIFLGSFYLVNLILAVVAMAYEEQNQATLEEAEQ				
Consensus	(401)	MIFFVLVIFLGSFYLVNLILAVVAMAYEEQNQATLEEAEQ				

——————————————————————————————————— Section 12

		441	450	460	470	480
ClareAJ251507protein	(441)	KEAEFQQMLEQLKKQQEEAQAVAAASAASRDFSGIGGLGE				
Translation of huNaIII18 (AK)	(441)	KEAEFQQMLEQLKKQQEEAQAVAAASAASRDFSGIGGLGE				
Translation of JeongAF225987	(441)	KEAEFQQMLEQLKKQQEEAQAVAAASAASRDFSG■GGLGE				
Consensus	(441)	KEAEFQQMLEQLKKQQEEAQAVAAASAASRDFSGIGGLGE				

——————————————————————————————————— Section 13

		481	490	500	510	520
ClareAJ251507protein	(481)	LLESSSEASKLSSKSAKEWRNRRKKRRQREHLEGNNKGER				
Translation of huNaIII18 (AK)	(481)	LLESSSEASKLSSKSAKEWRNRRKKRRRREHLEGNNKGER				
Translation of JeongAF225987	(481)	LLESSSEASKLSSKGAKEWRNRRKKRRQREHLEGNNKGER				
Consensus	(481)	LLESSSEASKLSSKSAKEWRNRRKKRRQREHLEGNNKGER				

——————————————————————————————————— Section 14

		521	530	540	550	560
ClareAJ251507protein	(521)	DSFPKSESEDSVKRSSFLFSMDGNRLTSDKKFCSPHQSLL				
Translation of huNaIII18 (AK)	(521)	DSFPKSESEDSVKRSSFLFSMDGNRLTSDKKFCSPHQSLL				
Translation of JeongAF225987	(521)	DSFPKSESEDSVKRSSFLFSMDGNRLTSDKKFCSPHQSLL				
Consensus	(521)	DSFPKSESEDSVKRSSFLFSMDGNRLTSDKKFCSPHQSLL				

Section 15

		561	570	580	590	600
ClareAJ251507protein	(561)	SIRGSLFSPRRNSKTSIFSFRGRAKDVGSENDFADDEHST
Translation of huNaIII18 (AK)	(561)	SIRGSLFSPRRNSKTSIFSFRGRAKDVGSENDFADDEHST
Translation of JeongAF225987	(561)	SIRGSLFSPRRNSKTSIFSFRGRAKDVGSENDFADDEHST
Consensus	(561)	SIRGSLFSPRRNSKTSIFSFRGRAKDVGSENDFADDEHST

Section 16

		601	610	620	630	640
ClareAJ251507protein	(601)	FEDSESRRDSLFVPHRHGERRNS-----------------
Translation of huNaIII18 (AK)	(601)	FEDSESRRDSLFVPHRHGERRNSNVSQASMSSRMVPGLPA
Translation of JeongAF225987	(601)	FEDGESRRDSLFVPHRHGERRNSNVSQASMSSRMVPGLPA
Consensus	(601)	FEDSESRRDSLFVPHRHGERRNSNVSQASMSSRMVPGLPA

Section 17

		641	650	660	670	680
ClareAJ251507protein	(624)	------------------------------NGTTTETE
Translation of huNaIII18 (AK)	(641)	NGKMHSTVDCNGVVSLVGGPSALTSPTGQLPPEGTTTETE
Translation of JeongAF225987	(641)	NGKMHSTVDCNGVVSLVGGPSALTSPTGQLPPEGTTTETE
Consensus	(641)	NGKMHSTVDCNGVVSLVGGPSALTSPTGQLPPEGTTTETE

Section 18

		681	690	700	710	720
ClareAJ251507protein	(632)	VRKRRLSSYQISMEMLEDSSGRQRAVSIASILTNTMEELE
Translation of huNaIII18 (AK)	(681)	VRKRRLSSYQISMEMLEDSSGRQRAVSIASILTNTMEELE
Translation of JeongAF225987	(681)	VRKRRLSSYQISMEMLEDSSGRQRAVSIASILTNTMEELE
Consensus	(681)	VRKRRLSSYQISMEMLEDSSGRQRAVSIASILTNTMEELE

Section 19

		721	730	740	750	760
ClareAJ251507protein	(672)	ESRQKCPPCWYRFANVFLIWDCCDAWLKVKHLVNLIVMDP
Translation of huNaIII18 (AK)	(721)	ESRQKCPPCWYRFANVFLIWDCCDAWLKVKHLVNLIVMDP
Translation of JeongAF225987	(721)	ESRQKCPPCWYRFANVFLIWDCCDAWLKVKHLVNLIVMDP
Consensus	(721)	ESRQKCPPCWYRFANVFLIWDCCDAWLKVKHLVNLIVMDP

Section 20

		761	770	780	790	800
ClareAJ251507protein	(712)	FVDLAITICIVLNTLFMAMEHYPMTEQFSSVLTVGNLVFT
Translation of huNaIII18 (AK)	(761)	FVDLAITICIVLNTLFMAMEHYPMTEQFSSVLTVGNLVFT
Translation of JeongAF225987	(761)	FVDLAITICIVLNTLFMAMEHYPMTEQFSSVLTVGNLVFT
Consensus	(761)	FVDLAITICIVLNTLFMAMEHYPMTEQFSSVLTVGNLVFT

Section 21

		801	810	820	830	840
ClareAJ251507protein	(752)	GIFTAEMVLKIIAMDPYYYFQEGWNIFDGIIVSLSLMELG
Translation of huNaIII18 (AK)	(801)	GIFTAEMVLKIIAMDPYYYFQEGWNIFDGIIVSLSLMELG
Translation of JeongAF225987	(801)	GIFTAEMVLKIIAMDPYYYFQEGWNIFDGIIVSLSLMELG
Consensus	(801)	GIFTAEMVLKIIAMDPYYYFQEGWNIFDGIIVSLSLMELG

Section 22

		841	850	860	870	880
ClareAJ251507protein	(792)	LSNVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVG
Translation of huNaIII18 (AK)	(841)	LSNVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVG
Translation of JeongAF225987	(841)	LSNVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVG
Consensus	(841)	LSNVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVG

Section 23

		881	890	900	910	920
ClareAJ251507protein	(832)	ALGNLTLVLAIIVFIFAVVGMQLFGKSYKECVCKINDDCT
Translation of huNaIII18 (AK)	(881)	ALGNLTLVLAIIVFIFAVVGMQLFGKSYKECVCKINDDCT
Translation of JeongAF225987	(881)	ALGNLTLVLAIIVFIFAVVGMQLFGKSYKECVCKINDDCT
Consensus	(881)	ALGNLTLVLAIIVFIFAVVGMQLFGKSYKECVCKINDDCT

Section 24

		921	930	940	950	960
ClareAJ251507protein	(872)	LPRWHMNDFFHSFLIVFRVLCGEWIETMWDCMEVAGQTMC
Translation of huNaIII18 (AK)	(921)	LPRWHMNDFFHSFLIVFRVLCGEWIETMWDCMEVAGQTMC
Translation of JeongAF225987	(921)	LPRWHMNDFFHSFLIVFRVLCGEWIETMWDCMEVAGQTMC
Consensus	(921)	LPRWHMNDFFHSFLIVFRVLCGEWIETMWDCMEVAGQTMC

Section 25

		961	970	980	990	1000
ClareAJ251507protein	(912)	LIVFMLVMVIGNLVVLNLFLALLLSSFSSDNLAATDDDNE
Translation of huNaIII18 (AK)	(961)	LIVFMLVMVIGNLVVLNLFLALLLSSFSSDNLAATDDDNE
Translation of JeongAF225987	(961)	LIVFMLVMVIGNLVVLNLFLALLLSSFSSDNLAATDDDNE
Consensus	(961)	LIVFMLVMVIGNLVVLNLFLALLLSSFSSDNLAATDDDNE

Section 26

		1001	1010	1020	1030	1040
ClareAJ251507protein	(952)	MNNLQIAVGRMQKGIDYVKNKMRECFQKAFFRKPKVIEIH
Translation of huNaIII18 (AK)	(1001)	MNNLQIAVGRMQKGIDYVKNKMRECFQKAFFRKPKVIEIH
Translation of JeongAF225987	(1001)	MNNLQIAVGRMQKGIDYVKNKMRECFQKAFFRKPKVIEIH
Consensus	(1001)	MNNLQIAVGRMQKGIDYVKNKMRECFQKAFFRKPKVIEIH

Section 27

		1041	1050	1060	1070	1080
ClareAJ251507protein	(992)	EGNKIDSCMSNNTGIEISKELNYLRDGNGTTSGVGTGSSV
Translation of huNaIII18 (AK)	(1041)	EGNKIDSCMSNNTGIEISKELNYLRDGNGTTSGVGTGSSV
Translation of JeongAF225987	(1041)	EGNKIDSCMSNNTGIEISKELNYLRDGNGTTSGVGTGSSV
Consensus	(1041)	EGNKIDSCMSNNTGIEISKELNYLRDGNGTTSGVGTGSSV

Section 28

		1081	1090	1100	1110	1120
ClareAJ251507protein	(1032)	EKYVIDENDYMSFINNPSLTVTVPIAVGESDFENLNTEEF
Translation of huNaIII18 (AK)	(1081)	EKYVIDENDYMSFINNPSLTVTVPIAVGESDFENLNTEEF
Translation of JeongAF225987	(1081)	EKYVIDENDYMSFINNPSLTVTVPIAVGESDFENLNTEEF
Consensus	(1081)	EKYVIDENDYMSFINNPSLTVTVPIAVGESDFENLNTEEF

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                                                                    ———— Section 29
                     (1121) 1121        1130        1140        1150        1160
  ClareAJ251507protein (1072) SSESELEESKEKLNATSSSEGSTVDVVLPREGEQAETEPE
Translation of huNaIII18 (AK) (1121) SSESELEESKEKLNATSSSEGSTVDVVLPREGEQAETEPE
Translation of JeongAF225987  (1121) SSESELEESKEKLNATSSSEGSTVDVVLPREGEQAETEPE
            Consensus (1121) SSESELEESKEKLNATSSSEGSTVDVVLPREGEQAETEPE
                                                                    ———— Section 30
                     (1161) 1161        1170        1180        1190        1200
  ClareAJ251507protein (1112) EDLKPEACFTEGCIKKFPFCQVSTEEGKGKIWWNLRKTCY
Translation of huNaIII18 (AK) (1161) EDLKPEACFTEGCIKKFPFCQVSTEEGKGKIWWNLRKTCY
Translation of JeongAF225987  (1161) EDFKPEACFTEGCIKKFPFCQVSTEEGKGKIWWNLRKTCY
            Consensus (1161) EDLKPEACFTEGCIKKFPFCQVSTEEGKGKIWWNLRKTCY
                                                                    ———— Section 31
                     (1201) 1201        1210        1220        1230        1240
  ClareAJ251507protein (1152) SIVEHNWFETFIVFMILLSSGALAFEDIYIEQRKTIKTML
Translation of huNaIII18 (AK) (1201) SIVEHNWFETFIVFMILLSSGALAFEDIYIEQRKTIKTML
Translation of JeongAF225987  (1201) SIVEHNWFETFIVFMILLSSGALAFEDIYIEQRKTIKTML
            Consensus (1201) SIVEHNWFETFIVFMILLSSGALAFEDIYIEQRKTIKTML
                                                                    ———— Section 32
                     (1241) 1241        1250        1260        1270        1280
  ClareAJ251507protein (1192) EYADKVFTYIFILEMLLKWVAYGFQTYFTNAWCWLDFLIV
Translation of huNaIII18 (AK) (1241) EYADKVFTYIFILEMLLKWVAYGFQTYFTNAWCWLDFLIV
Translation of JeongAF225987  (1241) EYADKVFTYIFILEMLLKWVAYGFQTYFTNAWCWLDFLIV
            Consensus (1241) EYADKVFTYIFILEMLLKWVAYGFQTYFTNAWCWLDFLIV
                                                                    ———— Section 33
                     (1281) 1281        1290        1300        1310        1320
  ClareAJ251507protein (1232) DVSLVSLVANALGYSELGAIKSLRTLRALRPLRALSRFEG
Translation of huNaIII18 (AK) (1281) DVSLVSLVANALGYSELGAIKSLRTLRALRPLRALSRFEG
Translation of JeongAF225987  (1281) DVSLVSLVANALGYSELGAIKSLRTLRALRPLRALSRFEG
            Consensus (1281) DVSLVSLVANALGYSELGAIKSLRTLRALRPLRALSRFEG
                                                                    ———— Section 34
                     (1321) 1321        1330        1340        1350        1360
  ClareAJ251507protein (1272) MRVVVNALVGAIPSIMNVLLVCLIFWLIFSIMGVNLFAGK
Translation of huNaIII18 (AK) (1321) MRVVVNALVGAIPSIMNVLLVCLIFWLIFSIMGVNLFAGK
Translation of JeongAF225987  (1321) MRVVVNALVGAIPSIMNVLLVCLIFWLIFSIMGVNLFAGK
            Consensus (1321) MRVVVNALVGAIPSIMNVLLVCLIFWLIFSIMGVNLFAGK
                                                                    ———— Section 35
                     (1361) 1361        1370        1380        1390        1400
  ClareAJ251507protein (1312) FYHCVNMTTGNMFDISDVNNLSDCQALGKQARWKNVKVNF
Translation of huNaIII18 (AK) (1361) FYHCVNMTTGNMFDISDVNNLSDCQALGKQARWKNVKVNF
Translation of JeongAF225987  (1361) FYHCVNMTTGNMFDISDVNNLSDCQALGKQARWKNVKVNF
            Consensus (1361) FYHCVNMTTGNMFDISDVNNLSDCQALGKQARWKNVKVNF
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                                                                            Section 36
                              (1401) 1401        1410        1420        1430      1440
        ClareAJ251507protein (1352) DNVGAGYLALLQVATFKGWMDIMYAAVDSRDVKLQPVYEE
   Translation of huNalII18 (AK) (1401) DNVGAGYLALLQVATFKGWMDIMYAAVDSRDVKLQPVYEE
   Translation of JeongAF225987  (1401) DNVGAGYLALLQVATFKGWMDIMYAAVDSRDVKLQPVYEE
                   Consensus (1401) DNVGAGYLALLQVATFKGWMDIMYAAVDSRDVKLQPVYEE
                                                                            Section 37
                              (1441) 1441        1450        1460        1470      1480
        ClareAJ251507protein (1392) NLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFNQQKKKFGG
   Translation of huNalII18 (AK) (1441) NLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFNQQKKKFGG
   Translation of JeongAF225987  (1441) NLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFNQQKKKFGG
                   Consensus (1441) NLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFNQQKKKFGG
                                                                            Section 38
                              (1481) 1481        1490        1500        1510      1520
        ClareAJ251507protein (1432) QDIFMTEEQKKYYNAMKKLGSKKPQKPIPRPANKFQGMVF
   Translation of huNalII18 (AK) (1481) QDIFMTEEQKKYYNAMKKLGSKKPQKPIPRPANKFQGMVF
   Translation of JeongAF225987  (1481) QDIFMTEEQKKYYNAMKKLGSKKPQKPIPRPANKFQGMVF
                   Consensus (1481) QDIFMTEEQKKYYNAMKKLGSKKPQKPIPRPANKFQGMVF
                                                                            Section 39
                              (1521) 1521        1530        1540        1550      1560
        ClareAJ251507protein (1472) DFVTRQVFDISIMILICLNMVTMMVETDDQGKYMTLVLSR
   Translation of huNalII18 (AK) (1521) DFVTRQVFDISIMILICLNMVTMMVETDDQGKYMTLVLSR
   Translation of JeongAF225987  (1521) DFVTRQVFDISIMILICLNMVTMMVETDDQGKYMTLVLSR
                   Consensus (1521) DFVTRQVFDISIMILICLNMVTMMVETDDQGKYMTLVLSR
                                                                            Section 40
                              (1561) 1561        1570        1580        1590      1600
        ClareAJ251507protein (1512) INLVFIVLFTGEFVLKLVSLRHYYFTIGWNIFDFVVVILS
   Translation of huNalII18 (AK) (1561) INLVFIVLFTGEFVL█LVSLRHYYFTIGWNIFDFVVVILS
   Translation of JeongAF225987  (1561) INLVFIVLFTGEFVLKLVSLRHYYFTIGWNIFDFVVVILS
                   Consensus (1561) INLVFIVLFTGEFVLKLVSLRHYYFTIGWNIFDFVVVILS
                                                                            Section 41
                              (1601) 1601        1610        1620        1630      1640
        ClareAJ251507protein (1552) IVGMFLAEMIEKYFVSPTLFRVIRLARIGRILRLIKGAKG
   Translation of huNalII18 (AK) (1601) IVGMFLAEMIEKYFVSPTLFRVIRLARIGRILRLIKGAKG
   Translation of JeongAF225987  (1601) IVGMFLAEMIEKYSVSPTLFRVIRLARIGRILRLIKGAKG
                   Consensus (1601) IVGMFLAEMIEKYFVSPTLFRVIRLARIGRILRLIKGAKG
                                                                            Section 42
                              (1641) 1641        1650        1660    ·   1670      1680
        ClareAJ251507protein (1592) IRTLLFALMMSLPALFNIGLLLFLVMFIYAIFGMSNFAYV
   Translation of huNalII18 (AK) (1641) IRTLLFALMMSLPALFNIGLLLFLVMFIYAIFGMSNFAYV
   Translation of JeongAF225987  (1641) IRTLLFALMMSLPALFNIGLLLFLVMFIYAIFGMSNFAYV
                   Consensus (1641) IRTLLFALMMSLPALFNIGLLLFLVMFIYAIFGMSNFAYV
```

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                                                                    ———— Section 43
            (1681)  1681         1690        1700        1710        1720
ClareAJ251507protein (1632)  KKEAGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILN
Translation of huNalll18 (AK) (1681)  KKEAGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILN
Translation of JeongAF225987  (1681)  KKEAGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILN
          Consensus (1681)  KKEAGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILN
                                                                    ———— Section 44
            (1721)  1721         1730        1740        1750        1760
ClareAJ251507protein (1672)  SAPPDCDPDTIHPGSSVKGDCGNPSVGIFFFVSYIIISFL
Translation of huNalll18 (AK) (1721)  SAPPDCDPDTIHPGSSVKGDCGNPSVGIFFFVSYIIISFL
Translation of JeongAF225987  (1721)  SAPPDCDPDTIHPGSSVKGDRGDPSVGIFFFVSYIIISFL
          Consensus (1721)  SAPPDCDPDTIHPGSSVKGDCGNPSVGIFFFVSYIIISFL
                                                                    ———— Section 45
            (1761)  1761         1770        1780        1790        1800
ClareAJ251507protein (1712)  VVVNMYIAVILENFSVATEESAEPLSEDDFEMFYEVVWEKF
Translation of huNalll18 (AK) (1761)  VVVNMYIAVILENFSVATEESAEPLSEDDFEMFYEVVWEKF
Translation of JeongAF225987  (1761)  VVVNMYIAVILENFSVATEESAEPLSEDDFEMFYEVVWEKF
          Consensus (1761)  VVVNMYIAVILENFSVATEESAEPLSEDDFEMFYEVVWEKF
                                                                    ———— Section 46
            (1801)  1801         1810        1820        1830        1840
ClareAJ251507protein (1752)  DPDATQFIEFSKLSDFAAALDPPLLIAKPNKVQLIAMDLP
Translation of huNalll18 (AK) (1801)  DPDATQFIEFSKLSDFAAALDPPLLIAKPNKVQLIAMDLP
Translation of JeongAF225987 (1801)  DPDATQFIEFSKLSDFAAALDPPLLIAKPNKVQLIAMDLP
          Consensus (1801)  DPDATQFIEFSKLSDFAAALDPPLLIAKPNKVQLIAMDLP
                                                                    ———— Section 47
            (1841)  1841         1850        1860        1870        1880
ClareAJ251507protein (1792)  MVSGDRIHCLDILFAFTKRVLGESGEMDALRIQMEDRFMA
Translation of huNalll18 (AK) (1841)  MVSGDRIHCLDILFAFTKRVLGESGEMDALRIQMEDRFMA
Translation of JeongAF225987 (1841)  MVSGDRIHCLDILFAFTKRVLCESGEMDALRIQMEDRFMA
          Consensus (1841)  MVSGDRIHCLDILFAFTKRVLGESGEMDALRIQMEDRFMA
                                                                    ———— Section 48
            (1881)  1881         1890        1900        1910        1920
ClareAJ251507protein (1832)  SNPSKVSYEPITTTLKRKQEEVSAAIIQRNFRCYLLKQRL
Translation of huNalll18 (AK) (1881)  SNPSKVSYEPITTTLKRKQEEVSAAIIQRNFRCYLLKQRL
Translation of JeongAF225987 (1881)  SNPSKVSYEPITTTLKRKQEEVSAAIIQRNFRCYLLKQRL
          Consensus (1881)  SNPSKVSYEPITTTLKRKQEEVSAAIIQRNFRCYLLKQRL
                                                                    ———— Section 49
            (1921)  1921         1930        1940        1950        1960
ClareAJ251507protein (1872)  KNISSNYNKEAIKGRIDLPIKQDMIIDKLNGNSTPEKTDG
Translation of huNalll18 (AK) (1921)  KNISSNYNKEAIKGRIDLPIKQDMIIDKLNGNSTPEKTDG
Translation of JeongAF225987 (1921)  KNISSNYNKEAIKGRIDLPIKQDMIIDKLNGNSTPEKTDG
          Consensus (1921)  KNISSNYNKEAIKGRIDLPIKQDMIIDKLNGNSTPEKTDG
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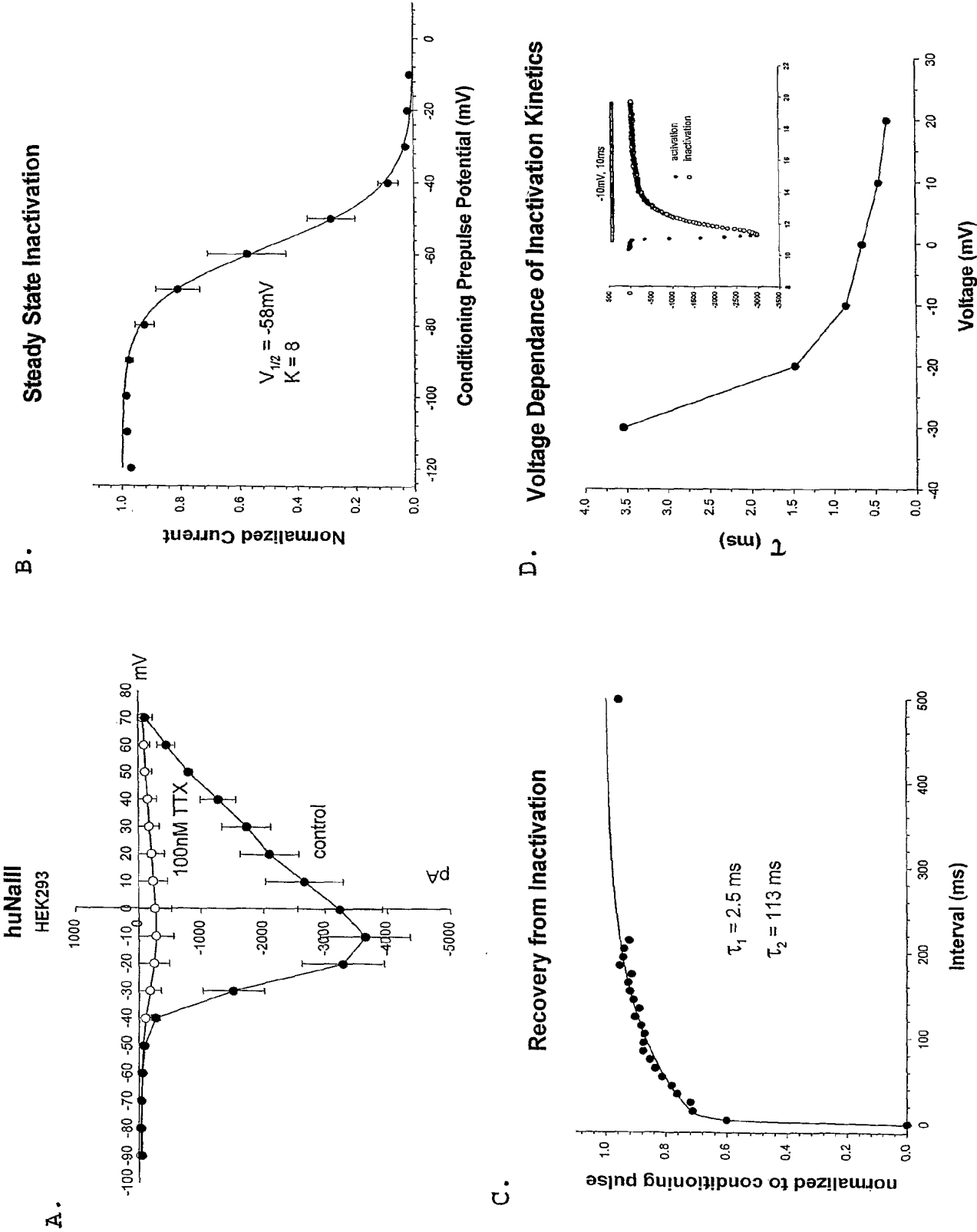
```
                                                                    ____ Section 50
                             (1961) 1961        1970      1980       1990      2000
ClareAJ251507protein  (1912) S S S T T S P P S Y D S V T K P D K E K F E K D K P E K E S K G K E V R E N Q K
Translation of huNalll18 (AK) (1961) S S S T T S P P S Y D S V T K P D K E K F E K D K P E K E S K G K E V R E N Q K
Translation of JeongAF225987  (1961) S S S T T P P P S Y D S V T K P D K E K F E K D K P E K E S K G K E V R E N Q K
Consensus (1961) S S S T T S P P S Y D S V T K P D K E K F E K D K P E K E S K G K E V R E N Q K
```

Figure 5

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant (for all designated States except US): **EURO-CELTIQUE S.A.** [LU/LU]; 122, Boulevard de la Petrusse, L-2330 Luxembourg (LU).

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(74) Agents: **ROBINSON, Joseph, R.** et al.; Darby & Darby P.C., P.O. Box 5257, New York, NY 10150-5257 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Published:
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(88) **Date of publication of the international search report:**
17 March 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SPLICE VARIANT OF HUMAN SODIUM III CHANNEL (HNAIII18)

(57) **Abstract:** Described herein is a splice variant of the human NaIII channel α subunit, designated hNaIII18. Also described are nucleotide and amino acid sequence for hNaIII18, oligonucleotide primers and probes for hNaIII18, hNaIII18 regulatory sequences, hNaIII18-specific antibodies, methods of detecting hNaIII18 proteins or nucleic acids, and methods of screening for modulators of hNaIII18 expression or activity.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/38796

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7)   :   C12 Q 1/68
US CL   :   435/6, 320.1, 325, 455, 91.41; 536/23.1, 23.2, 23.5, 24.3, 24.31
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/6, 320.1, 325, 455, 91.41; 536/23.1, 23.2, 23.5, 24.3, 24.31

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,110,672 A (MANDEL et al.) 29 August 2000 (29.08.2000), especially Examples.	1-21

☐ Further documents are listed in the continuation of Box C.　　☐ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 2004 (26.11.2004)	14 DEC 2004
Name and mailing address of the ISA/US 　　Mail Stop PCT, Attn: ISA/US 　　Commissioner for Patents 　　P.O. Box 1450 　　Alexandria, Virginia 22313-1450 Facsimile No. (703) 872-9306	Authorized officer 　Padmavathi v Baskar Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (July 1998)

Continuation of B. FIELDS SEARCHED Item 3:
WEST AND MEDLINE.
search terms: nucleotide, polypeptide, sodium channel, human.